Attorney's Docket No. 1018995-000452

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**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

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| In re Patent Application of | |
| Nishizumi Nishimuta et al. | Group Art Unit: 1618 |
| Application No.: 10/046,575 | Examiner: ZOHREH A FAY |
| Filed: January 16, 2002 | Appeal No.: _____ |
| For: EXTERNAL PREPARATION FOR SKIN DISEASES CONTAINING NITROIMIDAZOLE | |

## APPEAL BRIEF

**Mail Stop APPEAL BRIEF - PATENTS**
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This appeal is from the decision of the Primary Examiner dated February 20, 2007 finally rejecting claims 1, 13, 14 and 31, which are reproduced as the Claims Appendix of this brief.

☐ A check covering the ☐ $ 250 ☐ $ 500 Government fee is filed herewith.

☒ Charge ☐ $ 250 ☒ $ 500 to Credit Card. Form PTO-2038 is attached.

The Commissioner is hereby authorized to charge any appropriate fees under 37 C.F.R. §§1.16, 1.17, and 1.21 that may be required by this paper, and to credit any overpayment, to Deposit Account No. 02-4800.

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## Table of Contents

I. Real Party in Interest

The present application is assigned to SHOEI CO., LTD.

Assignee SHOEI CO., LTD. is the real party in interest with regard to Application No. 10/046,575.

II. Related Appeals and Interferences

The Appellants' legal representative, or assignee, does not know of any other appeal or interference that will affect or be directly affected by or have bearing on the Board's decision in the pending appeal.

III. Status of Claims

Claims 1, 13 and 14 – 31 are pending in the application. Claims 15 - 30 have been withdrawn from consideration. Claims 1, 13, 14 and 31 have been finally rejected, which is the subject of this appeal.

IV. Status of Amendments

No amendments have been filed subsequent to the final rejection now appealed. The claims were last amended in the Amendment and Reply filed May 26, 2006.

V. Summary of the Claimed Subject Matter

The claimed subject matter is directed to a method of therapeutically treating, prophylactically treating or ameliorating atopic dermatitis. Atopic dermatitis, is a specific form of dermatitis as generally described in the Background of the Invention at pages 1-2 of the Specification.

As recited in claim 1,the method comprises applying an external preparation to portions of the disease of a patient. *See, e.g.* Specification at page 73, line 16, to page 78, line 27, and the subsequent examples.

The external preparation comprises a nitroimidazole derivative comprising 2-(2-methyl-5-nitroimidazole-1-yl)ethanol (general name: metronidazole), a pharmaceutically acceptable salt thereof, an ester thereof or other derivatives thereof as an active ingredient; or 1-(2-ethylsulfonylethyl)-2-methyl-5-nitroimidazole (general name: tinidazole) or a pharmaceutically acceptable salt thereof as an active ingredient. *See, e.g.* Specification at page 11, line 24 to page 29, line 7, with particular reference to page 37, lines 6-8.

Dependant claim 31 recites that a concentration of the nitroimidazole derivative is 0.1 to 20 % by weight based on the amount of the preparation. *See*, Specification at page 41, lines 10 to 17.

The external preparations described in claim 1 have been found to significantly enhance the effectiveness of certain other kinds of compounds, even at concentrations where those compounds show no effectiveness alone. *See, e.g.*, Specification at page 11, lines 9-23. Accordingly, dependant claim 13 further recites a method of claim 1 further comprising applying one medicine selected from the group consisting of an antimycotic agent, antibacterial agent, sulfa, immunosuppressant, antiinflammatory agent, antibiotic, antiviral agent, metabolic antagonist, antihistamine, tissue repair promoter, vitamin, antiallergic, local anesthetic, hair agent and steroid simultaneously or separately with an interval to the disease. *See, e.g.*, Specification at page 29, line 14 to page 30, line 10.

Dependant claim 14 further recites that the additional agent is used at a concentration at which the agent itself does not demonstrate any pharmacological effect. *See, e.g.*, Specification at page 11, lines 9-23.

Below, Appellants show that the Office has failed to establish a prima facie case of obviousness against claim 1. Appellants further submit that at least claims 13 and 14 recite additional features of the method of claim 1 that were also not suggested by the prior art. In particular, beyond the lack of suggestion or any reasonable expectation of success of the method of claim 1 in the prior art, the synergistic effectiveness in treatment of atopic dermatitis by the combinations claimed in claims 13 and 14 was not appreciated or suggested by the prior art. Consequently, the features of claims 13 and 14 should be separately considered and d not stand or fall with claim 1.

VI. Grounds of Rejection to be Reviewed on Appeal

Claims 1, 13, 14 and 31 have been finally rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over PCT Publication No. WO 98/27960 ("Goodman") in view of the abstract of Fleischer, *Journal of Allergy and Clinical Immunology*, 104:S126-30, 1999 ("the Fleischer 1999 abstract") and the abstract of Miller et al., *Journal of Immunopharmacology*, 2:225-43, 1980 ("the Miller 1980 abstract.")

VII. Argument

The Office has not met its burden in making the rejection that is the subject of this appeal. To reject claims under 35 U.S.C. § 103, the Office bears the burden of establishing a *prima facie* case of obviousness based upon the prior art. The Examiner can satisfy this burden only by showing some objective teaching in the prior art or knowledge generally available to one of ordinary skill in the art that would *lead* that individual to combine the relevant teachings of the cited references in such a way as to have created the present invention at the time the application was filed. *See, e.g., In re Fine*, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988).

A. The prior art does not support a prima facie case of obviousness against claims 1, 13, 14 and 31.

The prior art fails to establish a proper *prima facie* case of obviousness. To establish a *prima facie* case of obviousness, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. M.P.E.P. § 2143; *In re Rouffet*, 149 F.3d 1350, 1355, 47 U.S.P.Q.2d 1453, 1458 (Fed. Cir. 1998) ("[T]the suggestion to combine requirement stands as a critical safeguard against hindsight analysis and rote application of the legal test for obviousness.") Rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness. *KSR Int'l Co. v. Teleflex Inc.*, ___ U.S. ___, 127 S.Ct. 1727, 1739, 82 U.S.P.Q.2d 1385, 1396 (April 30, 2007) (citing *In re Kahn*, 441 F.3d 977, 988, 78 U.S.P.Q.2d 1329 (Fed. Cir. 2006)).

The rejection under appeal is improper, because the rejection is premised upon mere conclusory statements alleging that the art taught something it clearly failed to teach. The

Examiner has persisted in maintaining the rejection relying on these unsupported conclusions despite Appellants presentation of sound scientific reasoning and explanation of what the cited art actually teaches.

As recited in claim 1, the claimed subject matter is directed to a method of therapeutically treating, prophylactically treating or ameliorating atopic dermatitis. Goodman teaches that a nitroimidazole gel composition comprising metronidazole or tinidazole can be used in the treatment of certain dermatological diseases, including rosacea and eczema, in which the skin becomes dry and inflamed. *Goodman* at 1. Goodman does not teach or suggest treating atopic dermatitis.

Dermatitis is the medical term for conditions characterized by inflammation of the skin. There are many different forms of dermatitis, including eczema and rosacea, that have different etiologies and treatments. Thus, a non-specific mention of dermatological disease does not constitute a suggestion to treat atopic dermatitis. Rosacea, which is taught by Goodman, is different from atopic dermatitis. Rosacea is a chronic disease affecting the skin of the nose, forehead, and cheeks marked by flushing, followed by red coloration due to dilation of the capillaries with papules and acne-like pustules. Eczema is an inflammatory skin disease with vesiculation, infiltration, watery discharge, and the development of scales and crusts. Even among eczemas, there are many different forms having different etiologies and treatments.

The Office correctly determined that treatments of different skin diseases are patentably distinct, particularly with respect to those that were recited in original claims 16-30 of the present application, "because each skin condition [is] caused by different etiology and the treatment could be different, as evidence by numerous documents." *Office Action mailed March 25, 2003*, at 2. In response to the restriction requirement that was premised upon this finding by the Office, Appellants elected without traverse the species of atopic dermatitis. *Reply filed April 24, 2003*, at 2. The Examiner made the restriction requirement that was based upon this determination final. *Office Action mailed July 16, 2003*, at 2. Therefore, in accordance with the Office's own findings, a treatment of any of the different forms of dermatitis does not suggest a treatment of another form of dermatitis, each type of dermatitis having a different etiology.

Goodman does not teach or suggest treating atopic dermatitis using an external preparation of metronidazole or tinidazole. Of the many different diseases falling under the

broad category of dermatitis, Goodman only demonstrated that a nitroimidazole gel composition comprising metronidazole or tinidazole can be used in the treatment of particular forms of eczema and rosacea.

The Fleischer 1999 abstract of a review of treatments of atopic dermatitis refers to the disadvantages of topical corticosteroids, which had been used because of their broad immunomodulatory effects, and relative advantages of tacrolimus in treating atopic dermatitis. However, neither corticosteroids nor tacrolimus are directly related to the compounds recited in the present claims. The Office has alleged that the Fleischer 1999 abstract teaches that immunosuppressants generally are effectively used in the treatment of atopic dermatitis. *Office Action dated July 16, 2003*, at 5. However, this generalization has been shown to be overly broad and not entirely true, and therefore would not have suggested the present invention to a person of ordinary skill in the art.

Contrary to the implication in the alleged basis for the rejection, Appellants respectfully submit that the Fleischer 1999 abstract does not support the conclusion that it would be obvious to try using any compound having immunosuppressive activity in an external preparation for the treatment of atopic dermatitis. The immune system was and is well known to be so complex that different disease conditions, such as the many different forms of dermatitis and eczema, can be caused by different kinds of immune disregulation. The particular cause of atopic dermatitis was, and still is, unknown. Specification at 2, lines 13-14. Therefore, a person of ordinary skill in the art would not know whether suppression of any particular aspect of immune response would have a desired affect on a particular condition. On the other hand, broad acting immune suppressants were known to cause undesired side effects as Fleischer indicated in the abstract. Thus, the Fleischer 1999 abstract can not be interpreted as suggesting using any compounds other than the particular compounds that had previously been found to be useful in treating atopic dermatitis. Moreover, the combination of the Fleischer abstract with Goodman still fails to suggest the combination proposed in the rejection.

The Miller 1980 abstract does not cure the deficiencies in the combination of the Fleischer 1999 abstract with Goodman. The Miller 1980 abstract refers to a scientific publication directed to a study of five imdiazole compounds in an *in vitro* system to test whether the compounds affected the response of human lymphocytes to compounds or cells that were known to promote blast transformation, a step in process of immune reaction

stimulation. The Examiner has alleged that the Miller 1980 abstract teaches that tinidazole is an effective immunosuppressant *in vivo*.

The Examiner has apparently misapprehended the Miller 1980 abstract. The Miller 1980 abstract does not show that any imidazole compounds can be used as immunosupressants *in vivo*, because the study described in the abstract is an *in vitro* study using cell cultures. Miller merely suggested that such studies could be used for screening compounds that might be investigated as immunosupressants *in vivo*. Miller does not suggest that the reported experiments are conclusive that any compound can be used in any treatment. Indeed some compounds, including those recited in claim 1 produced results suggesting immunostimulatory activity.

More particularly, with respect to the compounds recited in claim 1, tinidazole and metronidazole were actually reported by Miller to enhance the immune cells response to stimulation by plant mitogens. Thus, the results reported by Miller would suggest, if anything, that tinidazole and metronidazole could have immunostimulatory effects *in vivo*. Consequently, if the alleged implications of the Fleischer 1999 abstract under the theory propounded by the Office would have had any influence on a person of ordinary skill in the art, then the Miller study would have suggested that tinidazole and metronidazole were actually unsuitable. That is, the results reported by Miller are actually contrary to the alleged basis for the rejection.

Therefore, the combination of the Fleischer 1999 abstract and the Miller 1980 abstract with Goodman could not have lead to the present invention as the Office has alleged. Even if the conclusion that the Examiner alleged could be derived from the Fleischer 1999 abstract were correct, the Miller 1980 abstract would have suggested that tinidazole and metronidazole were not appropriate candidates for treatment of atopic dermatitis.

The Office has not met its burden to support the rejection and the rejection should be overruled, because the Examiner has failed to adduce a sound scientific principle within the knowledge of one of skill in the art that would have led from the prior art to the presently claimed combination.

A specific understanding or principle within the knowledge of a skilled artisan that would have motivated one to make the combination in the manner claimed is required to make out a proper *prima facie* case of obviousness. *In re Kotzab*, 217 F.3d 1365, 1369-70, 55 U.S.P.Q.2d 1313, 1318 (Fed. Cir. 2000). In other words, the Examiner must provide a

logical reason as disclosed in the prior art at the time of the invention for combining the references so as to arrive at the invention. Otherwise, the use of such teachings as evidence of obviousness must be considered impermissible hindsight. *See, e.g., In re Nomiya*, 509 F.2d 566, 184 U.S.P.Q. 607 (CCPA 1975); *Ex parte Stauber*, 208 U.S.P.Q. 945, 946 (Bd. Pat. App. & Intf. 1980). The Office has relied upon merely conclusory statements regarding the motivation and expectation of success allegedly provided by the asserted combination. These statements are not sufficient to meet the Office's burden of presenting a logical reason for the rejection that is supported by sound scientific evidence in the prior art.

Considering the so-called Graham factors, to the extent such an analysis is reflected in the conclusory statements of the Examiner, the analysis does not establish a case of obviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18, 148 U.S.P.Q. 459, 467 (1966). The differences between the prior art and the claimed subject matter includes that Goodman does not teach or suggest a treatment for atopic dermatitis. Rather Goodman is directed to treating eczema and rosacea.

The prior art teaches that atopic dermatitis is clearly distinguished in etiology and treatment from other types of dermatitis and eczema, indeed, atopic dermatitis is the most difficult form of dermatitis to treat. *See, e.g.*, WO 93/20817 (previously submitted in an IDS filed on May 17, 2004) ('the WO '817 publication"). The WO '817 publication describes a "treatment of inflammatory and/or infectious skin conditions of the eczema, acne and/or rosacea type" *Id.* at 6, lines 24-26. In particular, regarding the treatment of eczema, the WO '817 publication describes "[o]ne type of eczema which has been treated effectively in this way is the seborrhoeic variety" *Id.* at 6, lines 26-28. Thus, the WO '817 publication clearly evidences that the art describing eczema encompasses various types of dermatitis distinct from atopic dermatitis.

Like Goodman, while the WO '817 publication has working examples of treating distinct skin conditions, there are no working examples wherein atopic dermatitis is treated. Indeed, it is noted that one patient left the study due to periodic dermatitis. *Id.* at 9, lines 32-33. As another example, see PCT Publication No. WO 89/06537 ("the WO '537 publication")(cited in the IDS submitted March 8, 2002), which teaches a treatment of rosacea, other acne form conditions, and certain types of dermatitis using metronidazole. WO 89/06537, at 5, line 22-28. The WO '537 publication does not teach or suggest that this nitroimidazole compound could effectively treat any other type of dermatitis than the limited

conditions that are cited. In particular, while there are suggestions of treating different forms of skin disease using nitorimidazole compounds in the art, there is no suggestion of treating atopic dermatitis using metronidazole or tinidazole. Thus, it is clear that a person of ordinary skill in the art would not have considered that a treatment for the specific forms of dermatitis cited in the art could be generalized to an effective treatment of atopic dermatitis.

Indeed, effective treatment of atopic dermatitis is not the same or similar to other skin diseases. *See,* Specification at page 1, line 20 to page 2, line 25. The treatment of atopic dermatitis has been particularly difficult. *Id.* The cause of atopic dermatitis has not been determined and, although there are pharmaceutical compositions for treatment of atopic dermatitis on the market, those treatments have various drawbacks in side effects and lack of effectiveness. An effective pharmaceutical composition for the treatment of atopic dermatitis has been strongly desired for many years without satisfactory results prior to the present invention. *Id.* Not until applicants' invention has an effective pharmaceutical composition for the treatment of atopic dermatitis been developed. *Id.*

The Fleisher 1999 abstract does not suggest metronidazole or tinidazole for treatment of atopic dermatitis. The Fleischer 1999 abstract does not even suggest, as the Examiner has implied that broadly immunosuppressive compounds provide suitable treatment, because the Fleischer 1999 abstract notes particular problems with such treatments that are also noted in the present Specification. *See, e.g.,* Specification at page 2, lines 7-25. Even if a suggestion to treat atopic dermatitis using immunosuppressive drugs could be inferred from the Fleischer 1999 abstract, which is contradicted by the abstract itself, the Miller 1980 abstract does not indicate that metronidazole or tinidazole have appropriate immunomodulatory activities. Indeed, in the in vitro assay reported by Miller, metronidazole and tinidazole appeared to have immunostimulatory activities. Therefore, combining The Fleischer 1999 abstract and the Miler 1980 abstract with Goodman, would not have led a person of ordinary skill in the art to the present invention.

The Examiner has adduced no evidence that any general immunomodulatory activity would render metronidazole or tinidazole, or derivatives thereof, as obvious active ingredients in treating atopic dermatitis. While an immune reaction may have been implicated in the etiology of atopic dermatitis, the Examiner has failed to show that the state of the art was such that any general or specific activity of metronidazole or tinidazole would have suggested that those compounds were appropriate active ingredients specifically in a

treatment of atopic dermatitis prior to the invention of the methods presently claimed by Appellants.

Moreover, the use of tinidazole has been shown to provide surprising and unexpected benefits in treating atopic dermatitis not shown by any prior art treatment. Subsequent to Applicants' July 14, 2000, international filing date, it was reported that tacrolimus ointment cannot be used for the treatment of atopic dermatitis in patients with a high level nephropathy of hyperkalemia; in pregnant women or women suspecting pregnancy; and in patients receiving UV therapy such as PUVA therapy. Furthermore, as a rule, the tacrolimus ointment is not used for patients of dermal infectious diseases. By contrast, the present invention has none of these defects, and can be used to treat such patients.

Indeed, no effective treatment for atopic dermatitis was created prior to the present invention despite substantial efforts in the art. The Office has adduced no evidence that any person prior to the present inventors appreciated the possibility of the presently claimed methods of treating atopic dermatitis. Furthermore, as has been pointed out, the specification of the present application provides evidence of unexpected superior effects in the treatment of atopic dermatitis which is nowhere appreciated in the prior art. For example, the present specification includes Test Examples 3 (pages 147-148), 4 (pages 148-150), 7 (pages 153-154), and 8 (pages 155-156) wherein ointments or creams containing tinidazole were used to treat atopic dermatitis demonstrate that the present invention produces unexpected and superior effects.

Such unexpected results that demonstrate the superiority of the present invention over the combined state of the prior art are indicia of the non-obviousness of the present invention that have not received sufficient consideration by the Office. *See, e.g. In re Fouche*, 439 F.2d 1237, 1241, 169 USPQ 429, 433 (C.C.P.A. 1971); *In re Blondel*, 499 F.2d 1311, 1317, 182 U.S.P.Q. 293, 298 (C.C.P.A. 1974). The effectiveness that is demonstrated by the working examples of the specification and is nowhere evidenced in the prior art proves that the presently claimed methods could not have been obvious. The fact that such an effective treatment of atopic dermatitis is not evidenced in any prior art makes it clear that prior to the painstaking study by the present inventors that revealed the effectiveness of the claimed treatment, no one else had appreciated the possibility of meeting the long felt need for the presently claimed method. It is not enough that one of skill in the art would be aware of the individual elements comprising the invention. *See, In re Rouffet*, 149 F.3d 1350, 1355, 47

U.S.P.Q.2d 1453, 1458 (Fed. Cir. 1998) (Fed. Cir. 1998)("The examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed.")(emphasis added)).

B. Goodman teaches against Claims 13 and 14

Further distinguishing the teaching of Goodman from claims 13 and 14, Goodman actually teaches against combining metronidazole or tinidazole with any other active agent. Goodman at 7, lines 8-11. Thus, to the extent that Goodman teaches anything relevant to the present disclosure, Goodman teaches away from the combinations of claims 13 and 14 so that even if the Examiner's contentions with regard to the prior art were correct, there is evidence that it would not have been obvious to combine the compounds of claim 1 in the combinations recited in claims 13 and 14.

C. Conclusion

For at least the foregoing reasons, the rejection has not been properly made and should be overturned. Such action is respectfully requested.

## VIII. Claims Appendix

See attached Claims Appendix for a copy of the claims involved in the appeal.

## IX. Evidence Appendix

See attached Evidence Appendix for copies of evidence relied upon by Appellant.

## X. Related Proceedings Appendix

As there are no related proceedings identified in Section II, *supra*, no Related Proceedings Appendix is attached.

Respectfully submitted,

BUCHANAN INGERSOLL & ROONEY PC

Date August 20, 2007

By: _____
Christopher L. North
Registration No. 50433

P.O. Box 1404
Alexandria, VA 22313-1404
703 836 6620

# VIII. CLAIMS APPENDIX

**The Appealed Claims**

Claim 1 (Previously Presented): A method of therapeutically treating, prophylactically treating or ameliorating atopic dermatitis which comprises applying to portions of the disease of a patient an external preparation comprising

a nitroimidazole derivative comprising 2-(2-methyl-5-nitroimidazole-1-yl)ethanol (general name: metronidazole), a pharmaceutically acceptable salt thereof, an ester thereof or other derivatives thereof as an active ingredient; or 1-(2-ethylsulfonylethyl)-2-methyl-5-nitroimidazole (general name: tinidazole) or a pharmaceutically acceptable salt thereof as an active ingredient.

Claim 13 (Original): The method of claim 1 which comprises applying one compound of the nitroimidazole derivatives as defined in claim 1 and one medicine selected from the group consisting of an antimycotic agent, antibacterial agent, sulfa, immunosuppressant, antiinflammatory agent, antibiotic, antiviral agent, metabolic antagonist, antihistamine, tissue repair promoter, vitamin, antiallergic, local anesthetic, hair agent and steroid simultaneously or separately with an interval to the portions.

Claim 14 (Original): The method of claim 13, wherein the antimycotic agent, the antibacterial agent, the sulfa, the immunosuppressant, the antiinflammatory agent, the antibiotic, the antiviral agent, the metabolic antagonist, the antihistamine, the tissue repair promoter, the vitamin, the antiallergic, the local anesthetic, the hair agent or the steroids is used with a concentration at which the agent itself does not demonstrate any pharmacological effect.

Claim 31 (Original): The method of claim 1 wherein a concentration of the nitroimidazole derivative is 0.1 to 20 % by weight based on the amount of the preparation.

## IX. EVIDENCE APPENDIX

Appellants rely upon the following attached evidence:

| | |
|---|---|
| **A** | PCT Publication No. WO 98/27960 ("Goodman") (cited by the Office in stating the rejection under appeal) |
| **B** | The abstract of Fleischer, Journal of Allergy and Clinical Immunology, 104:S126-30, 1999 ("the Fleischer 1999 abstract") (cited by the Office in stating the rejection under appeal) |
| **C** | The abstract of Miller et al., J. of Immunopharmacology, 2:225-43, 1980 ("the Miller 1980 abstract.") (cited by the Office in stating the rejection under appeal) |
| **D** | PCT Publication No. WO 93/20817 ("the WO '817 publication")(cited in the IDS filed on May 17, 2004). |
| **E** | PCT Publication No. WO 89/06537 ("the WO '537 publication")(cited in the IDS filed on March 8, 2002) |

# ATTACHMENT A

**PCT** WORLD INTELLECTUAL PROPERTY ORGANIZATION
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 9/00 — A2

(11) International Publication Number: **WO 98/27960**

(43) International Publication Date: 2 July 1998 (02.07.98)

(21) International Application Number: PCT/GB97/03512

(22) International Filing Date: 19 December 1997 (19.12.97)

(30) Priority Data:
9626513.7 20 December 1996 (20.12.96) GB

(71) Applicant *(for all designated States except US)*: BIOGLAN IRELAND (R & D) LIMITED [IE/IE]; Unit 5, 151 Baldoyle Industrial Estate, Dublin 13 (IE).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: GOODMAN, Michael [GB/GB]; 30 Rushbrook Close, Ampthill, Bedfordshire MK45 2XE (GB). LINDAHL, Åke [SE/SE]; Ringduvevagen 50, S–274 33 Skurup (SE).

(74) Agent: JUMP, Timothy, John, Simon; Venner, Shipley & Co., 20 Little Britain, London EC1A 7DH (GB).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

**Published**
*Without international search report and to be republished upon receipt of that report.*

(54) Title: A NITROIMIDAZOLE GEL COMPOSITION

(57) Abstract

A viscous hydrogel composition, for use in a topical treatment of a skin condition involving dry or inflammed skin, comprising an antimicrobially active nitroimidazole drug, a water miscible alkylene glycol, a hydroxyalkyl cellulose gelling agent and water, buffered to have a physiologically acceptable pH and a method of making the same.

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# A NITROIMIDAZOLE GEL COMPOSITION

## DESCRIPTION

The present invention relates to viscous, jelly or cream like, pharmaceutical compositions for skin application, preferably for use in topical treatments of skin which is intolerant of exposure to aqueous preparations of non-physiological pH, or of excessive hypo- or hypertonicity. The invention also relates to a method of preparing such compositions.

Antimicrobially active imidazole derivatives, such as the nitroimidazole compounds metronidazole and tinidizole, can be used in the topical treatment of certain dermatological diseases, including rosacea and eczema, in which the skin becomes dry or inflamed, or is predisposed to becoming dry or inflamed when exposed to aqueous media. Dry or inflamed skin is highly intolerant of exposure to water based formulations with a pH outside the physiologically acceptable range of approximately pH 5-6, or which exert a physiologically incompatible osmotic pressure. Thus, topically applied aqueous compositions with an inappropriately high or low pH, or which exert an incompatible osmotic pressure, not only have the potential to cause irritation and stinging, but their use can actually worsen the symptoms of a disease.

With some active agents, this problem can be overcome by employing oil based formulations. However, many antimicrobially active imidazole derivatives are

substantially insoluble in such non-polar vehicles and, therefore, cannot be formulated in this manner.

One known aqueous based metronidazole gel composition includes lactic acid both as an humectant and in order to increase the solubility of the metronidazole. However, the presence of lactic acid in this formulation causes it to have a low pH and to be prone to causing an unacceptable degree of irritation to dry, sensitive or disease inflamed skin.

Other known topical metronidazole formulations include cross-linked polymers of acrylic acid, sold under the registered trade mark CARBOPOL, as thickening agents. Although it is possible to use such thickeners to prepare gels with a pH in the range of 5-6, unless great care is exercised during the manufacture of formulations employing these materials, they can form clumps which are insoluble, due to the formation of a water impregnable layer around the clump interior, and which cannot be reduced or dissolved once formed. In such circumtances, hydration of the resin will be incomplete and the result can be broad pH fluctuations in the final product. Moreover, polyacrylic acid resins are sensitive to salts and cations and are not stable in the presence of more than about 0.1% of strongly ionizable salts, particularly those with multivalent cations, such as calcium, magnesium, iron and aluminium salts. Thus, not only is it difficult to manufacture such formulations consistently within an acceptable (narrow) pH range, but it may

also be impossible to include therein a sufficient amount of ionic material to achieve an ideal pH, mitigate clumping induced pH variation, or to achieve a skin compatible osmotic pressure.

An object of the present invention is to provide a viscous composition useful in the topical treatment of highly sensitive skin with water soluble active agents, such as metronidazole, which is less prone to irritate inflamed or sensitive skin and which is more easily and more readily manufactured than known such products.

In a first aspect, the present invention provides a method for preparing a viscous hydrogel composition comprising a pharmaceutically active agent, a polysaccharide, a water-miscible organic solvent and water, said method comprising the steps of suspending the polysaccharide in the water-miscible organic solvent and mixing the resulting suspension into an aqueous medium thereby to hydrate the polysaccharide and to form a viscous hydrogel composition. The polysaccharide, preferably acts as a gelling or thickening agent. An advantage of this aspect of the invention is that it enables clumping of the polysaccharide, and consequential broad pH fluctuations in the final product, to be avoided and thereby allows the aforementioned object of the invention to be achieved.

Preferably, the aqueous medium comprises a previously formed aqueous solution of the pharmaceutically active agent. Alternatively or additionally, the active agent

can be mixed with the water-miscible organic solvent before the suspension is mixed with the aqueous medium. In this alternative procedure, the active agent can be suspended or dissolved in the water-miscible organic solvent and is preferably mixed therewith before the polysaccharide is suspended therein.

The active agent can be dissolved in water at a temperature of 15-50°C, 25-40°C and, preferably, 35-40°C (to provide the aqueous medium) and the suspension of polysaccharide can be at a temperature of 4-30°C, preferably 15-25°C, or 4-15°C, preferably 10-15°C, immediately prior to mixing with the aqueous medium. It is preferred for the polysaccharide to be insoluble or substantially insoluble in the organic solvent.

In an embodiment of the first aspect of the invention, the active agent is antimicrobially active nitroimidazole drug. Preferably, the polysaccharide is a non-ionic cellulose ester, ether, hydroxy-ether, or hydroxy-ester, or a non-ionic starch derivative. The polysaccharide can be a methyl, ethyl or propyl cellulose ester, ether, hydroxy-ether or hydroxy-ester. Preferably, the polysaccharide is a hydroxyalkyl cellulose. Preferably, the water-miscible organic solvent is an alkylene glycol.

In accordance with a second aspect of the present invention there is provided a viscous hydrogel composition, for use in a topical treatment of a skin condition

involving dry or inflammed skin, comprising an antimicrobially active nitroimidazole drug, a water miscible alkylene glycol, a hydroxyalkyl cellulose gelling agent and water, buffered to have a physiologically acceptable pH.

Since they can be manufactured using processes, such as those according to the first aspect of the invention, which allow clumping to be avoided, an advantage of compositions in accordance with this aspect of the invention is that they can be produced consistently and within an acceptably narrow pH range.

In a third aspect, the invention provides a viscous hydrogel composition, for use in a topical treatment of a skin condition involving dry or inflammed skin, prepared or preparable by a method in accordance with the first aspect of the invention.

Unlike previous compositions, compositions in accordance with the second aspect of the invention are, and those prepared in accordance with the first aspect can be, buffered, for example by the inclusion therein of ionic buffers such as conventional weak acid/salt buffers. By so doing, it is easy to ensure that such compositions will have a pH within a physiologically acceptable pH range, and that any tendency they otherwise could have to clumping induced pH variation, or pH drift during storage and after application to the skin, is mitigated or reduced below an acceptable limit.

Accordingly, in embodiments of all the aspects of the invention, suitable buffering agents are selected so that the pH of and, in some embodiments, the osmotic pressure exerted by the composition is physiologically acceptable, not only immediately on application to the skin but, preferably, also for a sufficient period thereafter to prevent irritation through pH (or osmotic pressure) drift after application to the skin.

Suitable buffers include acetic acid/acetate, hydrochloric acid/citrate, citro-phosphate, phosphate, phosphate buffered saline, and citric acid/citrate systems. The preferred buffering agents are citric acid and a citrate, preferably sodium citrate, and, in preferred embodiments, the inventive composition has a pH within the range of 4.5-6.5, preferably within the range of 5-6 and, more preferably, of about 5.5. In preferred embodiments of the first aspect of the invention, buffering agents are included in the aqueous medium before the suspended polysaccharide thickening agent is mixed with said solution.

Preferably, the method in accordance with the first aspect of the invention is employed to prepare a composition in accordance with the second aspect of the invention.

The hydroxyalkyl cellulose gelling agent can be hydroxymethyl, hydroxyethyl or hydroxypropyl cellulose. The preferred such agent is hydroxyethyl cellulose.

It is preferred that the hydroxyalkyl cellulose gelling agent is insoluble or substantially insoluble in the water miscible alkylene glycol (when substantially pure). Suitable alkylene glycols include glycerol, dipropylene glycol, polyethylene glycol, propylene carbonate, propylene glycol, butylene glycol, pentylene glycol and hexylene glycol. The preferred alkylene glycol is propylene glycol.

It is preferred that the nitroimidazole drug is the sole pharmaceutically active agent used in methods and compositions in accordance with the invention. Metronidazole or tinidazole are the preferred nitroimidazole drugs, the most preferred being metronidazole.

Preferred embodiments of the invention have a viscosity within the range of 10,000 and preferably 50,000 to 200,000 cps.

Preferably, compositions in accordance with or prepared by the invention are for use in treating skin conditions involving dry or inflamed skin, including rosacea, eczema and conditions involving infections responsive to anti-microbially active imidazole derivatives such as metronidazole. The latter include those conditions which are caused or exacerbated by organisms responsive to anti-microbially active imidazole derivatives, including infected fungating tumors and benign cutaneous ulcers.

It is preferred that compositions in accordance with or prepared by the invention exert a physiologically acceptable osmotic pressure.

In a further aspect, the invention provides the use of a composition in accordance with the second or third aspect of the invention or a composition prepared by a method in accordance with the first aspect of the invention, for the preparation of a medicament for use in treating a skin condition involving dry or inflamed skin, including rosacea, eczema and conditions involving infections responsive to anti-microbially active nitroimidazole derivatives, preferably metronidazole (the latter including those conditions which are caused or exacerbated by organisms responsive to anti-microbially active imidazole derivatives). In another aspect, the invention comprises the use of a nitroimidazole drug for the preparation of a medicament in accordance with the second or third aspect of the invention, for use in treating a skin condition involving dry or inflamed skin, preferably one of the aforementioned conditions.

In a yet further aspect, the invention provides a method of treating a skin condition involving dry or inflammed skin, preferably rosacea, eczema or a condition involving an infection responsive to an antimicrobially active nitroimidazole drug, preferably metronidazole, comprising topically applying a composition in

accordance with the second or third aspect of this invention to skin effected by said condition.

Preferred, non-limiting examples of the invention, in its various aspects, will now be described.

Example 1

The materials employed in this example are set out in the following table.

| | | |
|---|---|---|
| Metronidazole | 0.75% | |
| Water | to 100% | |
| Citric acid | Q.S. | To provide pH 5.5 |
| Sodium Citrate | Q.S. | |
| Hydroxyethyl Cellulose | 1.8% | |
| Propylene Glycol | 5.0% | |
| Methyl-p-benzoic acid ester | 0.15% | |
| Propyl-p-benzoic acid ester | 0.05% | |

In a first vessel, the metronidazole is dissolved in the water at a temperature of 35-40°C and sufficient quantities of the buffering agents, citric acid and sodium citrate, are then added to the resulting solution, to provide the finished composition with a pH of 5.5. Conventional preservatives (not listed above) may also be included in the solution.

In a separate vessel, the preservatives methyl-p-benzoic acid ester and propyl-p-benzoic acid ester are dissolved in the propylene glycol and the hydroxyethyl cellulose is added to the resulting solution, to form a suspension. This suspension is then cooled to 10-15°C and then added to the first vessel, containing the buffered aqueous metronidazole solution, while the latter is vigorously stirred. Stirring is continued until the hydroxyethyl cellulose is fully hydrated. After the resulting mixture has become homogenous, it is allowed to stand for one day and the resulting gel is then packed.

Example 2

The same materials are employed in this example in the same quantities as are employed in Example 1 above. Sufficient quantities of citric acid and sodium citrate are dissolved in the required amount of water to provide the finished composition with a pH of 5.5. Conventional preservations (not listed) can be included in this solution. In a separate vessel, the methyl-p-benzoic acid ester and the propyl-p-benzoic acid ester are dissolved in the propylene glycol, and the metronidazole followed by the hydroxyethyl cellulose are added to the resulting solution, to form a suspension. This suspension is then cooled to 10-15°C and added to a second vessel containing the citrate buffered aqueous solution, while the latter is vigorously stirred. Stirring is continued until the hydroxyethyl cellulose is

fully hydrated. After the resulting mixture has become homogenous, it is allowed to stand for one day and the resulting gel is then packed.

Example 3-12

Further compositions are made up using the materials and methods described in Examples 1 and 2, but with the citric acid and sodium citrate being replaced with acetic acid and sodium acetate (examples 3 and 4), hydrochloric acid and sodium citrate (examples 5 and 6), disodium hydrogen orthophosphate and citric acid (examples 7and 8), disodium hydrogen orthophosphate and potassium dihydrogen orthophosphate (examples 9 and 10), and disodium hydrogen orthophosphate, potassium dihydrogen orthophosphate and sodium chloride (examples 11 and 12), respectively.

Example 13

Twelve patients suffering from rosacea with mild to severe erythema and a minimum of three pustules or papules on the face were treated with a 0.75% metronidazole gel over a period of nine weeks. The metronidazole gel was topically applied on a twice daily basis. By week nine, the papule/pustule count was reduced by 50% or more in all patients, with 100% clearing in 75% of the patients. The degree of erythema exhibited by all of the patients in the group improved significantly, from being relatively severe at the outset to being relatively mild at the end of the nine week period of the test.

## CLAIMS

1. A method of preparing a viscous hydrogel composition comprising a pharmaceutically active agent, a polysaccharide, a water-miscible organic solvent and water, comprising the steps of suspending the polysaccharide in the water-miscible organic solvent and mixing the resulting suspension into an aqueous medium thereby to hydrate the polysaccharide and to form a viscous hydrogel composition.

2. A method as claimed in claim 1, wherein the pharmaceutically active agent is dissolved in the aqueous medium, or suspended or dissolved in the water miscible organic solvent, before said suspension is mixed with said aqueous medium.

3. A method as claimed in claim 2, wherein the pharmaceutically active agent is suspended or dissolved in the water-miscible organic solvent, before the polysaccharide is suspended therein.

4. A method as claimed in claim 2, wherein the pharmaceutically active agent is dissolved in the aqueous medium at a temperature of 15-50°C, 25-40°C, or 35-40°C.

5. A method as claimed in any of claims 1-4, wherein the polysaccharide suspension is at a temperature of 4-30°C, preferably 15-25°C, or 4-15°C, preferably 10-15°C, immediately prior to mixing with the aqueous medium.

6. A method as claimed in any of claims 1-5, wherein the pharmaceutically active agent is a nitroimidazole drug.

7. A method as claimed in claim 6, wherein the nitroimidazole drug is metronidazole or tinidazole and, preferably metronidazole.

8. A method as claimed in any of claims 1-7, wherein the composition is buffered to have a physiologically acceptable pH.

9. A method as claimed in claim 8, wherein a buffer is included in the aqueous medium, preferably before the suspended polysaccharide is mixed with said medium.

10. A method as claimed in claim 8, or claim 9, wherein the buffer comprises an acetic acid/acetate, hydrochloric acid/citrate, citric acid/citrate, citro-phosphate, phosphate, or phosphate buffered saline, buffer system.

11. A method as claimed in claim 10, wherein the buffer system comprises citric acid and a citrate, preferably sodium citrate.

12. A method as claimed in any of claims 1-11, wherein the composition has a pH within the range of 4.5-6.5, preferably within the range of 5-6 and, more preferably, of about 5.5.

13. A method as claimed in any of claims 1-12, wherein the polysaccharide is non-ionic cellulose ester, ether, hydroxy-ether, or hydroxy-ester, or a non-ionic starch derivative.

14. A method as claimed in any of claims 1-13, wherein the polysaccharide is a hydroxyalkyl cellulose.

15. A method as claimed in claim 13 wherein the polysaccharide is a methyl, ethyl or propyl cellulose ester, ether, hydroxy-ether, or hydroxy-ester.

16. A composition as claimed in claim 14, wherein the hydroxyalkyl cellulose is hydroxymethyl, hydroxyethyl or hydroxypropyl cellulose, preferably, hydroxyethyl cellulose.

17. A method as claimed in any of claims 1-16, wherein the polysaccharide is insoluble or substantially insoluble in the water miscible organic solvent.

18. A method as claimed in any of claims 1-17, wherein the water-miscible organic solvent is a water miscible alkylene glycol.

19. A method as claimed in claim 18, wherein the water miscible alkylene glycol is glycerol, dipropylene glycol, propylene glycol, butylene glycol, pentylene glycol or hexylene glycol, and, preferably, propylene glycol.

20. A viscous hydrogel composition, for use in a topical treatment of a skin condition involving dry or inflammed skin, prepared or preparable by a method as claimed in any of claims 1-19.

21. A viscous hydrogel composition, for use in a topical treatment of a skin condition involving dry or inflammed skin, comprising an antimicrobially active nitroimidazole drug, a water miscible alkylene glycol, a hydroxyalkyl cellulose gelling agent and water, buffered to have a physiologically acceptable pH.

22. A composition as claimed in claim 21, devoid of any additional pharmaceutically active agent or agents.

23. A composition as claimed in claim 22, wherein the antimicrobially active nitroimidazole drug is the sole pharmaceutically active agent.

24. A composition as claimed in any of claims 20-23, wherein the hydroxyalkyl cellulose gelling agent is hydroxymethyl, hydroxyethyl or hydroxypropyl cellulose and, preferably, hydroxyethyl cellulose.

25. A composition as claimed in any of claims 20-24, wherein the antimicrobially active nitroimidazole drug is metronidazole or tinidazole, and preferably metronidazole.

26. A composition as claimed in any of claims 20-25 further comprising an acetic acid/acetate, hydrochloric acid/citrate, citric acid/citrate, citro-phosphate, phosphate, or phosphate buffered saline, buffer system.

27. A composition as claimed in claim 26 comprising citric acid and a citrate, preferably sodium citrate, as buffering agents.

28. A composition as claimed in any of claims 20-27 having a viscosity within the range of 10,000 and preferably 50,000 to 200,000 cps.

29. A composition as claimed in any of claims 20-28 having a pH within the range of 4.5-6.5, preferably within the range of 5-6 and, more preferably, of about 5.5.

30. A composition as claimed in any of claims 20-29, wherein the skin condition is rosacea, eczema or involves an infection responsive to the antimicrobially active nitroimidazole drug, preferably metronidazole.

31. A composition as claimed in any of claims 20-30, wherein the hydroxyalkyl cellulose gelling agent is insoluble or substantially insoluble in the water miscible alkylene glycol.

32. A composition as claimed in any of claims 20-31, wherein the water miscible alkylene glycol is glycerol, dipropylene glycol, propylene glycol, butylene glycol, pentylene glycol or hexylene glycol, and, preferably, propylene glycol.

33. A method as claimed in any of claims 1-18, wherein the composition is in accordance with any one of claims 21-32.

34. Use of a composition as claimed in any of claims 20-32 for the preparation of a medicament for use in treating a skin condition involving dry or inflamed skin,

preferably rosacea, eczema or a condition involving an infection responsive to an antimicrobially active nitroimidazole drug, preferably metronidazole.

35. Use of a nitroimidazole drug for the preparation of a medicament as claimed in any of claims 20-32 for use in treating a skin condition involving dry or inflamed skin, preferably rosacea, eczema or a condition involving an infection responsive to an antimicrobially active nitroimidazole drug, preferably metronidazole.

36. A method of treating a skin condition involving dry or inflammed skin, preferably rosacea, eczema or a condition involving an infection responsive to an antimicrobially active nitroimidazole drug, preferably metronidazole, comprising topically applying a composition as claimed in any of claims 20-32 to skin effected by said condition.

# ATTACHMENT B

Copy 2.

L7 ANSWER 11 OF 15 CAPLUS COPYRIGHT 2003 ACS
AN 1999:676812 CAPLUS
DN 131:280868
TI Treatment of **atopic dermatitis**: role of tacrolimus ointment as a topical noncorticosteroidal therapy
AU Fleischer, Alan B., Jr.
CS the Department of Dermatology, Wake Forest University School of Medicine, Winston-Salem, NC, 27157-1071, USA
SO Journal of Allergy and Clinical Immunology (1999), 104(3, Pt. 2), S126-S130
CODEN: JACIBY; ISSN: 0091-6749
PB Mosby, Inc.
DT Journal; General Review
LA English
CC 1-0 (Pharmacology)
AB A review with 30 refs. **Atopic dermatitis** is a chronic, relapsing form of **eczema** characterized by scaling, itchy, inflamed skin that can be triggered by an interplay of genetic, immunol., and environmental factors. Immune dysregulation appears to play an important role in the cause of **atopic dermatitis**. Topical corticosteroid agents have been the mainstay of therapy for **atopic dermatitis** because of their broad immunomodulatory effects. However, topical corticosteroid agents are not ideal agents because when used over the long term, they may cause cutaneous atrophy and **immunosuppression**. Systemic corticosteroidal agents, certain antihistaminic agents, systemic cyclosporin, and phototherapy have proven value in treating patients with **atopic dermatitis**. In the search for a noncorticosteroidal topical agent, tacrolimus stands out as being uniquely suited for this condition. Tacrolimus affects a broad spectrum of inflammatory mediators and processes known to be relevant to **atopic dermatitis** pathogenesis. Tacrolimus demonstrates good percutaneous penetration and appears to have no potential to cause cutaneous atrophy. There are multiple double-blind, controlled studies demonstrating the safety and efficacy of this agent in treating **atopic dermatitis**. The agent may be of particular benefit in children, among whom an alternative to the chronic use of corticosteroid agents, either topically or systemically, is highly desirable.
ST review tacrolimus **atopic dermatitis** immunosupression
IT Dermatitis
(atopic; treatment of **atopic dermatitis**: role of tacrolimus ointment as a topical noncorticosteroidal therapy)
IT **Immunosuppressants**
Pharmacodynamics
Pharmacokinetics
(treatment of **atopic dermatitis**: role of tacrolimus ointment as a topical noncorticosteroidal therapy)
IT 104987-11-3, Tacrolimus
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(treatment of **atopic dermatitis**: role of tacrolimus ointment as a topical noncorticosteroidal therapy)
RE.CNT 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE.
(1) Alaiti, S; J Am Acad Dermatol 1998, V38, P69 MEDLINE
(2) Aoyama, H; Br J Dermatol 1995, V133, P494 MEDLINE
(3) Boguniewicz, A; J Allergy Clin Immunol 1998, V102, P637
(4) de Paulis, A; J Invest Dermatol 1992, V99, P723 CAPLUS
(5) de Prost, Y; Acta Dermato-Venereologica Supplementum 1989, V144, P136 MEDLINE
(6) De Rie, M; Acta Derm Venereol 1991, V71, P452 MEDLINE

# ATTACHMENT C

Copy #1

L28 ANSWER 3 OF 6 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 81094292 EMBASE
DN 1981094292
TI Effects of simple imidazoles on human peripheral blood lymphocytes stimulated by mitogen or allogeneic cells.
AU Miller J.J.; Reeves S.C.; Salaman J.R.
CS K.R.U.F., Inst. Renal Dis., Cardiff Roy. Infirm., Cardiff, United Kingdom
SO Journal of Immunopharmacology, (1980) 2/2 (225-243).
CODEN: JOIMD6
CY United States
DT Journal
FS 030 Pharmacology
037 Drug Literature Index
026 Immunology, Serology and Transplantation
025 Hematology
LA English
AB Five imidazole compounds were added to cultures of human lymphocytes which had been stimulated to undergo blast transformation by exposure to phytohaemagglutinin, pokeweed mitogen or allogeneic cells. Two compounds, clotrimazole and dacarbazine (DTIC) produced a dose related suppression of these responses. Nimorazole was largely inactive whereas metronidazole and **tinidazole** actually enhanced the response - at least in those cultures stimulated by the plant mitogens. It is suggested that experiments of this kind are helpful in identifying those imidzaole compounds that could be used as **immunosuppressants** in vivo.
CT Medical Descriptors:
*allogenic cell
*lymphocyte transformation
*immunosuppressive treatment
*lymphocyte
*lymphocyte culture
thymidine h 3
in vitro study
human cell
blood and hemopoietic system
normal human
lymphatic system
Drug Descriptors:
*clotrimazole
*dacarbazine
*imidazole derivative
*metronidazole
*nimorazole
*tinidazole
niridazole
phytohemagglutinin
pokeweed mitogen
radioisotope
nagoxin
unclassified drug
RN (clotrimazole) 23593-75-1; (dacarbazine) 4342-03-4; (metronidazole) 39322-38-8, 443-48-1; (nimorazole) 6506-37-2; (tinidazole) 19387-91-8; (niridazole) 61-57-4; (phytohemagglutinin) 9008-97-3; (pokeweed mitogen) 63231-57-2
CN Ambilhar; Simplotan; Nagoxin; Canesten
CO May and baker (United Kingdom); Bayer (United Kingdom); Wellcome (United Kingdom); Pfizer (United Kingdom); Amersham (United Kingdom); Gibco (United Kingdom); Montedison (United Kingdom)

L28 ANSWER 5 OF 6 CAPLUS COPYRIGHT 2003 ACS
AN 1993:116260 CAPLUS
DN 118:116260
TI Effect of tinidazole on in vitro lymphokine production
AU Shaheen, Sajida; Rani, T. S. Hephzibah; Begum, Shahnaz; Ishaq, M.
CS Dep. Genet., Osmania Univ., Hyderabad, 500007, India
SO Medical Science Research (1993), 21(1), 19
CODEN: MSCREJ; ISSN: 0269-8951
DT Journal
LA English
CC 1-5 (Pharmacology)
AB Tinidazole concn.-dependently decreased the prodn. of leukocyte migration-inhibiting factor by phytohemagglutinin-activated human T-cells in vitro. This suggests that the drug is indeed immunosuppressive.
ST lymphocyte lymphokine formation tinidazole; leukocyte migration inhibiting factor lymphocyte tinidazole; **immunosuppression tinidazole**
IT **Immunosuppressants**
(**tinidazole** as)
IT Lymphocyte
(T-cell, leukocyte migration-inhibiting factor prodn. by human, tinidazole inhibition of)
IT Lymphokines and Cytokines
RL: FORM (Formation, nonpreparative)
(leukocyte migration-inhibiting factor, formation of, by human T-lymphocyte, tinidazole inhibition of)
IT 19387-91-8, Tinidazole
RL: BIOL (Biological study)
(leukocyte migration-inhibiting factor formation by human T-lymphocyte inhibition by)

# ATTACHMENT D

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International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : A61K 31/415 — A1

(11) International Publication Number: WO 93/20817

(43) International Publication Date: 28 October 1993 (28.10.93)

(21) International Application Number: PCT/SE93/00276

(22) International Filing Date: 31 March 1993 (31.03.93)

(30) Priority data:
9201188-1 14 April 1992 (14.04.92) SE

(71) Applicant *(for all designated States except US)*: HYDRO PHARMA SVERIGE AB [SE/SE]; P.O. Box 50310, S-202 13 Malmö (SE).

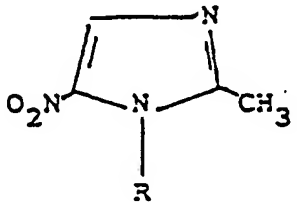
(72) Inventor; and
(75) Inventor/Applicant *(for US only)* : SJÖLUND, Eilert [SE/SE]; Köpmangatan 4B, S-871 30 Härnösand (SE).

(74) Agent: AWAPATENT AB; Box 45086, S-104 30 Stockholm (SE).

(81) Designated States: AT, AU, BB, BG, BR, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, US, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
*With international search report.*
*In English translation (filed in Swedish).*

(54) Title: NOVEL USE OF NITROIMIDAZOLES




(I)

(57) Abstract

The use of a compound of formula (I) wherein R is: a) $-(CH_2)_mSO_2(CH_2)_nCH_3$ where m = 2-3 and n = 0-1; or b) $-(CH_2)_mSO_2CH(CH_3)_2$ where m = 2-3 for the preparation of a pharmaceutical composition for the treatment, especially the topical treatment, of inflammatory and/or infectious skin conditions.

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Novel use of nitroimidazoles.

## Technical Field

The present invention relates to a novel pharmaceutical use of a specific group of imidazoles known per se in the past and also known in a medical context. More particularly, the invention relates to the use of the above compounds for the preparation of a pharmaceutical composition for the treatment of inflammatory and/or infectious skin conditions.

## Background of the invention

Acne vulgaris is a disease state which is distinguished by infected and blocked up sebaceous glands with inflammation in the surrounding tissue.

Acne often commences with hyperproliferation of corneocytes and the formation of an adhesive generating structure which binds the corneocytes together and forms a plug in the sebaceous gland canal. These closed comedones, also known as "whiteheads", are the first stage of acne. The closed comedones develop further into open comedones, "blackheads", or to inflammatory lesions of the papula or pustule type. These can then deepen and form cystic acne. Common to all of these conditions is the presence of large numbers of Proprionibacterium acnes, P. acnes.

The treatment of acne is diversified. Superficial and moderately severe acne, acne vulgaris, is locally treated especially with benzoyl peroxide, antibiotics and vitamin A derivatives. Benzoyl peroxide gives a complete recovery in around 60% of cases, but often causes side effects in the form of redness, irritation and dryness. An increase

in the frequency of a cancer, melanoma, after treatment with benzoyl peroxide is currently under discussion in the literature (see Jones G.R.N, Human Toxicology, (1985) 77: pp 413-421, "Skin Cancer: Risk to Individuals"). Antibiotics provide recovery frequencies of the same order of magnitude as for benzoyl peroxide. Lately, falling efficacy linked to the development of resistance has been mooted. Vitamin A derivatives have good efficacy against acne except for local side effects and even teratogenic effects.

Rosacea, previously known as acne rosacea, is a disease state which is distinguished by superficial inflamation, especially in the face. Nowadays, rosacea is treated inter alia with metronidazole.

Seborrhoea is a disease state which is distinguished by desquamating skin, often in conjunction with itching. In severe cases, a crust is formed which gives rise to mixed infections. Seborrhoeic eczema can be regarded partly as an inflammatory reaction and partly as an infection of Pitosporum ovale. Treatment nowadays is with steroids and in simpler cases with selenium sulphide and metronidazole.

In summary, it is apparent that the currently used remedies all exhibit one or more drawbacks as regards the abovementioned disease states.

As foreshadowed above, the compounds which are used according to the present invention are known per from the past. In this connection, the following can be named as examples of references describing the compounds and their preparation:

M.W. Miller, H.L. Howes and A.R. English, Antimicrobial Agents and Chemotherapy, 1969, pp 257-260, "Tinidazole, a potent new antiprotozoal agent";

H. Beckman, Drug Therapy 1963-64, pp 383-384, "Vaginal

trichomoniasis and monoiliasis";

G. Berkelhammer and G. Asato, (1968) Science 162: 1146 "2-amino-5-(1-methyl-5-nitro-2-imidazoyl)-1,2,4-thiadizole: A new microbial agent";

H.L. Howes et al., Antimicrobial Agents and Chemotherapy, 1969, pp 261-266, "Tinidazole, a new antiprotozoal agent"; and

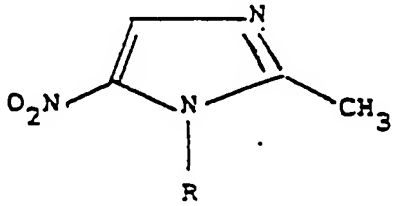
J. Azawa et al., (1965) J.Med.Chem. 8: pp150-153, "Substituent constants for aliphatic..."

Additionally, as regards the efficacy of tinidazole against parasites, for example, a description appears in "Tinidazole: A rew...", (1976) Drugs 11: pp423-440.

## Description of the invention

The present invention relates to a novel medical use of known pharmaceutically active substances and more particularly to the use of these for the preparation of a pharmaceutical composition for the treatment or prophylaxis of inflammatory and/or infectious skin conditions or diseases of the type mentioned above. Aside from providing a useful alternative to the abovementioned forms of treatement, the compounds used in accordance with the present invention also enable the elimination or at least reduction of the drawbacks or side effects arising in relation to the known remedies. They are, moreover, of particular interest against a combination of infection and inflammation.

In more concrete terms, the use of the invention relates to the use of a compound of the formula (I)




(I)

wherein R is:

a) $-(CH_2)_mSO_2(CH_2)_nCH_3$
where m = 2-3 and n = 0-1; or

b) $-(CH_2)_mSO_2CH(CH_3)_2$
where m = 2-3

for the preparation of a pharmaceutical composition for the treatment, especially the topical treatment, of inflammatory and/or infectious skin conditions.

Compounds used in accordance with the invention within variant a) are:

methyl(2-(2-methyl-5-nitro-1-imidazolyl)ethyl)sulfone (m = 2, n = 0);
ethyl(2-(2-methyl-5-nitro-1-imidazolyl)ethyl)sulfone (m = 2, n = 1);
methyl(2-(2-methyl-5-nitro-1-imidazolyl)propyl)sulfone (m = 3, n = 0); and
ethyl(2-(2-methyl-5-nitro-1-imidazolyl)propyl)sulfone (m = 3, n = 1).

Compounds within variant b) used in accordance with the invention are:

isopropyl(2-(2-methyl-5-nitro-1-imidazolyl)ethyl)sulfone (m = 2); and
isopropyl(2-(2-methyl-5-nitro-1-imidazolyl)propyl)sulfone (m = 3).

Of the above compounds, the use of ethyl(2-(2-methyl-5-nitro-1-imidazolyl)ethyl)sulfone is particularly preferred.

As indicated above, the compounds used in the practice of the invention are known per se from the past and therefore can be obtained direct from commercial sources or prepared by techniques that are in themselves known, e.g. by analogy to the preparative methods recited in the above mentioned references.

The amount or concentration of the compound used is, of course, selected on the basis of the infectious or inflammatory condition which is to be treated. However, a preferred concentration of the compounds in question is 0.25 to 5 weight percent, calculated on the total weight of the composition, a particularly favoured concentration regime being 0.5 to 2 weight percent, calculated on the same basis.

In other respects the pharmaceutical composition can be prepared by techniques that are in themselves known using known additives, depending on the desired mode of application. Topical application is considered of primary importance in this connection with the preferred modes of application being creams, gels and emulsions. Preparative methods for these dosage forms are, of course, described in innumerable references and need not be further recited here.

A particularly preferred dosage form, however, is one employing "hydrophilic solid crystals". Production of these is described, inter alia, in British patent publication 1,174,672 to which reference is made in this connection.

Generally speaking, however, the latter process requires blending a polar lipid which has the capacity to form said hydrophilic crystals with water or any other polar liquid with corrresponding properties such as glycerol, ethylene glycol or propylene glycol to form a mixture with a

concentration of water or other polar liquid of 50 to 59 weight percent. This mixture is brought to a temperature over the "transition temperature" for the particular lipid, this temperature being defined as the lowest temperature at which a lipid particle in contact with excess water or said polar liquid can absorb water or said polar liquid and be converted to cylindrical or spherical particles, "liposomes", exhibiting strong birefringency. The mixture is maintained over said temperature, with agitation, until conversion has taken place and then cooled under continued agitation to room or some other desired temperature, such that surface active solid crystals are formed. The compound of formula (I) used in accordance with the invention can be added before the lipid in question has been converted to liposomes or while it is still in liposome form.

Examples of conventional additives which can be incorporated in the pharmaceutical composition used in accordance with the invention are conventional carriers, consistency agents or regulators, pH regulators etc.

Particularly preferred embodiments of the invention involve the use of a compound of formula (I) for the treatment of inflammatory and/or infectious skin conditions of the eczema, acne and/or rosacea type. One type of eczema which has been treated effectively in this way is the seborrhoeic variety. In particular, it is thus apparent that the use of the invention can be employed against conditions having their origin in an infectious and an inflammatory component.

Examples

The invention will now be further illustrated with reference to the following non-limiting examples where various dose forms are exemplified.

Example 1

A cream preparation containing the following components was prepared:

| | |
|---|---|
| 1-glycerol monolaurate | 7 wt% |
| 1-glycerol monomyristate | 21 wt% |
| Propylene glycol | 30 wt% |
| Tinidazole | 2 wt% |
| Purified water to | 100 wt% |

Buffering systems, tensides and consistency agents can be incorporated in the cream for cosmetic purposes.

The cream was prepared in the following manner. The ingredients were mixed and the mixture heated to 70°C. After 15 minutes at this temperature, the mixture was cooled to room temperature at a rate of 1 - 3°C per minute.

The cream was tested on eight patients with moderately severe acne. Former treatments had been terminated at least one week before the treatment of the invention was initiated. Efficacy was evaluated on the basis of the number of papulae and pustules on the face and compared with historical data. Treatment was carried out for 2 - 5 weeks in contrast to the usual 8 weeks which formed the basis of the historical data (see Tables 1 & 2). No side effects were evident. One patient left the study due to periodic dermatitis.

TABLE 1

Calculation of the reduction in number of papulae and pustules

| Patient no. | Before | | After | |
|---|---|---|---|---|
| | Papulae | Pustules | Papulae | Pustules |
| 1 | 72 | 3 | 12 | 0 |
| 2 | 18 | 13 | 36 | 0 |
| 3 | 20 | 0 | 0 | 0 |
| 4 | 29 | 20 | 30 | 2 |
| 5 | 32 | 4 | 11 | 1 |
| 6 | 37 | 1 | 0 | 0 |
| 7 | 46 | 1 | 6 | 0 |
| 8 | 37 | 1 | 16 | 0 |
| Total | 451 | 43 | 115 | 3 |
| Percent reduction | | | 74.4 | 93.0 |

TABLE 2.

Overall Assessment

| | Patients | Doctor's assessment |
|---|---|---|
| Much better | 3 (37%) | 0-25% - |
| Noticeably better | 4 (50%) | 26-50% 1 |
| Better | - | 51-75% 4 |
| Unchanged | 1 (13%) | 76-100%3 |
| Worse | - | |
| Much worse | - | |

Example 2

A gel containing the following ingredients was prepared in the same manner as described in Example 1.

| | | |
|---|---|---|
| Tinidazole | 2 | wt% |
| Propylene glycol | 20 | wt% |
| Thickening agent | 0.5 | wt% |
| Purified water to | 100 | wt% |

The gel was given to patients with seborrhoeic eczema on the scalp. Earlier therapy with known agents had not had any result. When using the gel of Example 2, the patients became symptom free with 2 to 3 applications per week.

Example 3

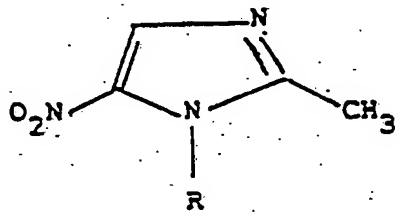
An emulsion with the following composition was prepared:

| | | |
|---|---|---|
| Liquid paraffin | 30 | g |
| Sorbitan mono-oleate | 1 | g |
| Polyoxyethylene (20) stearate | 1 | g |
| Water | 65.6 | g |
| Carbomer | 0.4 | g |
| Tinidazole | 2 | g |

The liquid paraffin was mixed with the sorbitan mono-oleate, heated to 70°C and tinidazole then mixed in. The polyoxyethylene (20) stearate, water and carbomer were mixed, homogenized and heated to 70°C. Under vigourous homogenizing, the different partial mixtures were mixed and the temperature allowed to drop to room temperature.

## CLAIMS

1. Use of a compound of the formula (I)



(I)

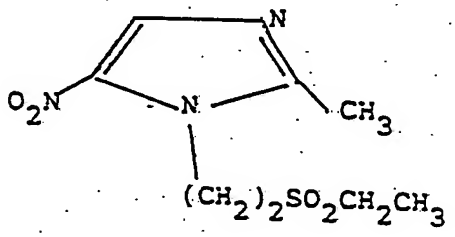
wherein R is:

a) $-(CH_2)_mSO_2(CH_2)_nCH_3$
where m = 2-3 and n = 0-1; or

b) $-(CH_2)_mSO_2CH(CH_3)_2$
where m = 2-3

for the preparation of a pharmaceutical composition for the treatment, especially the topical treatment, of inflammatory and/or infectious skin conditions.

2. The use of a compound of the formula (I) according to claim 1, wherein the compound is ethyl(2-(2-methyl-5-nitro-1-imidazolyl)ethyl)sulfone with the formula:



3. The use of a compound of the formula (I) according to claim 1 or 2 for the preparation of a pharmaceutical composition for the treatment of eczema, especially seborrhoeic eczema.

4. The use of a compound of the formula (I) according to claim 1 or 2 for the preparation of a pharmaceutical composition for the treatment of acne.

5. The use of a compound of the formula (I) according to claim 1 or 2 for the preparation of a pharmaceutical composition for the treatment of rosacea.

6. The use of a compound of the formula (I) according to any one of the preceding claims, wherein the compound is present in the composition in a concentration of 0.25 to 5 weight percent, calculated on the total weight of the composition.

7. The use of a compound of the formula (I) according to claim 6, wherein the concentration of the compound is 0.5 to 2 weight percent, calculated on the total weight of the composition.

8. The use of a compound of the formula (I) according to any one of claims 1 to 7 for the preparation of a pharmaceutical composition in the form of solid surface active crystals.

9. A method for the treatment of inflammatory and/or infectious skin conditions which comprises the administration, preferably topically, of a compound of the formula (I) in a pharmaceutical composition as defined in any one of claims 1 to 8 to a patient afflicted with such a condition.

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 93/00276

A. CLASSIFICATION OF SUBJECT MATTER

IPC5: A61K 31/415
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC5: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS-ONLINE, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X,Y | WO, A1, 9203133 (BLOOM LEONARD ET AL), 5 March 1992 (05.03.92) -- | 1-8 |
| Y | WO, A1, 8806888 (CURATEK PHARMACEUTICALS, INC.), 22 Sept 1988 (22.09.88) -- -------- | 1-8 |

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 11 June 1993 | 14 -07- 1993 |
| Name and mailing address of the ISA/<br>Swedish Patent Office<br>Box 5055, S-102 42 STOCKHOLM<br>Facsimile No. +46 8 666 02 86 | Authorized officer<br><br>Göran Karlsson<br>Telephone No. +46 8 782 25 00 |

Form PCT/ISA/210 (second sheet) (July 1992)

# INTERNATIONAL SEARCH REPORT

International Application No.
PCT/SE 93/00276

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 9
because they relate to subject matter not required to be searched by this Authority, namely:

A method for treatment of the human or animal body by therapy, see rule 39.1

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

30/04/93

International application No.
PCT/SE 93/00276

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| WO-A1- 9203133 | 05/03/92 | AU-A- 6405290 | 17/03/92 |
| WO-A1- 8806888 | 22/09/88 | AU-B- 610495 | 23/05/91 |
| | | AU-A- 7233787 | 10/10/88 |
| | | EP-A,B- 0305380 | 08/03/89 |
| | | SE-T3- 0305380 | |

# ATTACHMENT E

**PCT** WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 4 : A61K 31/78, 31/415 — A1

(11) International Publication Number: WO 89/ 06537

(43) International Publication Date: 27 July 1989 (27.07.89)

(21) International Application Number: PCT/US89/00116

(22) International Filing Date: 12 January 1989 (12.01.89)

(31) Priority Application Number: 144,252

(32) Priority Date: 15 January 1988 (15.01.88)

(33) Priority Country: US

(71) Applicant: CURATEK PHARMACEUTICALS, INC. [US/US]; 1965 Pratt Boulevard, Elk Grove Village, IL 60007 (US).

(72) Inventor: BORGMAN, Robert, J. ; 1735 Victoria Road, Mundelein, IL 60060 (US).

(74) Agents: CEPURITIS, Talivaldis; Dressler, Goldsmith, Shore, Sutker & Milnamow, Ltd., 1800 Prudential Plaza, Chicago, IL 60606 (US) et al.

(81) Designated States: AT (European patent), AU, BE (European patent), CH (European patent), DE (European patent), FR (European patent), GB (European patent), IT (European patent), JP, KR, LU (European patent), NL (European patent), SE (European patent).

**Published**
*With international search report.*

(54) Title: TOPICAL METRONIDAZOLE FORMULATIONS AND THERAPEUTIC USES THEREOF

(57) Abstract

Topical aqueous single-phase compositions containing metronidazole are disclosed. The compositions have improved specific activity and are substantially non-comedogenic, non-irritating and non-skin-drying. These aqueous topical compositions are particularly useful for treating rosacea and other acneform dermatological conditions, and certain forms of dermatitis.

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# TOPICAL METRONIDAZOLE FORMULATIONS AND THERAPEUTIC USES THEREOF

## Cross-Reference to Related Application

This application is a continuation-in-part of copending application U.S. Serial No. 819,066, filed on January 15, 1986.

## Technical Field

This invention relates to novel topical compositions containing metronidazole and methods of treating skin disorders using the same.

## Background of the Invention

Metronidazole, 1-(2-hydroxyethyl)-2-methyl-5-nitroimidazole, is a drug known to be effective in treating a variety of disorders. For example, the drug has direct trichomonacidal and amebacidal activity against Trichomonas vaginalis and Entamoeba histolytica, and is useful in combatting infections caused by those microbial parasites. Metronidazole has also been reported to be effective (via both oral and topical application) in treating skin disorders such as rosacea, ulcers infected with anaerobic bacteria, including decubitus ulcers (bed or pressure sores), venous ulcers, and diabetic foot ulcers, and other anaerobic infections such as post operative sepsis. There have also been reports that metronidazole is effective against perioral dermatitis.

Although oral administration of the drug has been employed for the treatment of certain disorders, long-term oral administration of the drug in cases of chronic disorders such as rosacea may be associated with certain unwanted side effects, and subjects all organ systems needlessly to high drug concentrations. Well-known problems associated with

systemic antibiotic therapy include gastro-intestinal intolerance and vaginitis. Thus, topical compositions are generally preferred for dermatological applications. See, for example, "Practical Advice Offered On Rosacea", Dermatology News, (April, 1985).

When formulating topical compositions for application to diseased skin, different aspects, such as thermodynamic activity of the drug in the base material vehicle, i.e., the affinity of drug to the vehicle, the release rate of the drug from the vehicle, the type and status of the skin, and the sensitization and irritation potential of components, are factors that can affect the therapeutic effectiveness of topical dermatological preparations. In the case of non-diseased skin with its intact stratum corneum, cell membrane-controlled penetration of the drug occurs. Therefore, a high thermodynamic activity of the drug in the vehicle is desirable, i.e., the drug has a low affinity to the vehicle, and therefore has a high rate of cell membrane penetration to promote transfer of the drug across the epidermal cell membranes. With diseased skin, the release rate of the drug from the vehicle generally is rate-determining for penetration into a patient's cells. Therefore, vehicles which dissolve the drug and have a low diffusional resistance are preferred. In general, drug concentration in the vehicle, and thus the degree of saturation, is considered to be a key formulation factor when optimizing topical delivery for maximum bioavailability.

Rosacea, formerly called Acne rosacea, is a chronic skin disease primarily affecting adults, with recurring symptoms that include erythema, papules,

pustules, rhinophyma, and telangiectses, primarily in the region of the nose, cheeks, and forehead. In rosacea, other acneform conditions, and certain types of dermatitis, topical treatment compositions are usually applied to both unafflicted and diseased areas. It is therefore desirable that a treatment have a mitigating effect on the diseased tissue and a prophylactic effect to prevent extension of involvement to the unafflicted tissue. Therefore, the preferred vehicles, and hence compositions, to obtain these desirable effects should contain metronidazole in a high thermodynamic activity and with a fast rate of release from the vehicle. Aqueous compositions of metronidazole would appear to meet the above criteria. However, the low solubility of metronidazole in water and several other solvents inhibits the preparation of an aqueous compositions. This has resulted in the development of oil-based, rather than aqueous, metronidazole compositions.

These current topical compositions generally are creams (oil in water emulsions) or ointments (petroleum jelly based compositions) with metronidazole being dissolved in the oil phase. The oils, certain surfactants and emulsifiers, and/or other ingredients utilized in the compositions have been found to be comedogenic, acnegenic, and/or irritating to the skin. See Fulton et al., Amer. Acad. of Dermatology 10(1):96-105, (Jan. 1984). Patients treated with such compositions therefore often experience skin problems which include irritation, uncomfortable drying of the skin, and "stinging" or "burning" sensations. In addition, the drug is generally dissolved or dispersed in the oil phase of such preparations, which reduces the specific activity of the drug due to inhibition of

drug transfer across the cell membrane. See "Treatment Of Rosacea With 1% Metronidazole Cream. A Double-Blind Study", Nielsen, P., British J. of Dermatology 108:327-332 (1983).

Thus, a need remains for metronidazole-containing dermatological preparations suitable for topical use which avoid the problems of current compositions. Such dermatological preparations would be useful for treating skin disorders such as rosacea and certain types of dermatitis, including perioral dermatitis. The present invention provides such preparations.

## Summary of the Invention

In accordance with the present invention, an aqueous gel composition for topical application comprises (a) a therapeutically effective amount of metronidazole, (b) a water-dispersible polycarboxylated vinyl polymer in an amount effective to gel said composition, and (c) an aqueous solvent for the metronidazole. Such compositions are single-phase aqueous gels that provide a relatively high specific activity of metronidazole as compared to prior art oil-based compositions and provide increased bioavailability of the metronidazole. The present compositions are constituted by substantially non-comedogenic, non-irritating ingredients and thus avoid problems associated with the use of prior art formulations in the treatment of skin diseases.

The gel-form compositons of the present invention minimize "pooling" and "running" of the contained medication, e.g., pooling into facial creases, which sometimes occurs with dermatological cream preparations. The resulting local excesses of the creams may contribute to problematic erythema or stinging. The gel-form compositions of the present

invention afford more control in application, and better maintenance of a uniform distribution of the drug over the area to be treated, than would generally be expected if the drug were applied as a cream or in an aqueous solution.

The gel advantageously functions as a "sustained delivery" system for the metronidazole, in which the drug continuously is delivered to the cells at, or slightly above, a minimum therapeutically effective level which is sustained over a period of time. This mode of drug release from the vehicle is preferred over vehicles which release the drug at levels much higher than the necessary therapeutic level shortly after application to the skin, followed by a sharp decrease to a level which is not therapeutically effective. The aqueous gel compositions of the present invention function as sustained delivery systems, whereas prior art formulations generally do not provide sustained drug delivery at a relatively constant therapeutically effective level over a period of time.

In one aspect, the present invention therefore provides a method for the prophylactic or therapeutic treatment of humans afflicted with such skin disorders as rosacea, other acneform conditions, e.g., acne vulgaris, steroid acne, acne conglobata, or nodulocystic acne, or certain types of dermatitis, e.g., perioral dermatitis or seborrheic dermatitis.

Numerous other advantages and features of the present invention will become readily apparent from the following description of the preferred embodiments of the invention, the accompanying examples, the drawings and the appended claims.

Brief Description of the Drawings

In the figures forming a part of the disclosure;

FIGURE 1 is a graph illustrating the in-vitro release of metronidazole from a gel composition (0.75 wt-% metronidazole; contains propylene glycol; pH about 5.8) over a 60-minute time period. Data points for Trial One are designated by (o), for Trial Two (•) and for Trial Three by (x);

FIGURE 2 is a graph illustrating the average release of metronidazole for the three trials shown in FIGURE 1;

FIGURE 3 is a graph illustrating the in-vitro release of metronidazole from another gel composition (0.75 wt-% metronidazole; no propylene glycol; pH about 5.8) over a 60-minute time period. Data points for Trial One are designated by (o), for Trial Two by (•) and for Trial Three by (x);

FIGURE 4 is a graph illustrating the average release of metronidazole for the three trials shown in FIGURE 3;

FIGURE 5 is a graph illustrating the in-vitro release of metronidazole from a cream composition (1.0 wt-% metronidazole; pH about 3.2) over a 60-minute time period. Data points for Trial One are designated by (o), for Trial Two by (•) and for Trial Three by (x);

FIGURE 6 is a graph illustrating the average release of metronidazole for the tree trials shown in FIGURE 5;

FIGURE 7 is a graph illustrating the average in-vitro release of metronidazole over a 60-minute time period. Data points for a gel composition (0.75 wt-% metronidazole containing propylene glycol; pH about 5.8) are designated by (o), for another gel

composition (0.75 wt-% metronidazole; no propylene glycol; pH about 5.8) by (x) and for a cream composition (1.0 wt-% metronidazole; pH about 3.2) by (●).

Description of Preferred Embodiments

While this invention is susceptible to embodiment in many different forms, there are shown in the drawings and will be described in detail, preferred embodiments of the invention. It should be understood, however, that the present disclosure is to be considered as an exemplification of the principles of this invention and is not intended to limit the invention to the embodiments illustrated.

The drug 1-(2-hydroxyethyl)-2-methyl-5-nitroimidazole and varous derivatives thereof are described in U.S. Patent No. 2,944,061, to Jacob et al., incorporated herein by reference.

The term "metronidazole" as used in this specification and claims is meant to include not only 1-(2-hydroxyethyl)-2-methyl-5-nitroimidazole, but also those analogs and derivatives of metronidazole which are solubilized in the gel compositions described herein and which have therapeutic activity when topically applied.

Substantially oil-free, aqueous compositions of metronidazole, in which the drug is solubilized in a single-phase aqueous gel, are disclosed. The overall advantages of such aqueous compositions in treating skin disorders have been discussed above, and are presented in greater detail herein below.

Metronidazole is employed in the compositions in a therapeutically effective amount. The actual concentration of metronidazole may vary, depending on the nature and degree of the disorders being treated, and whether the drug is being

administered for therapeutic or prophylatic purposes. The compositions advantageously comprise at least about 0.1 wt-% metronidazole, based on the total weight of the composition. Preferably metronidazole is present in an amount of about 0.25% to about 1.0%, and more preferably about 0.75% by weight, based on the total weight of the composition.

In the compositions of the present invention, metronidazole is dissolved in an aqueous solution of a high molecular weight polycarboxylated vinyl polymer. The polymer imparts a desirable viscous, gelled consistency to the composition when mixed with metronidazole and water. The gel compositions contain at least about 95% by weight water, based on the total weight of the composition, and have the requisite degree of metronidazole concentration, and hence thermodynamic activity, for effective topical delivery and bioavailability of metronidazole. The gel compositions of the present invention also have the requisite therapeutic activities as previously described.

The gel-forming polymer useful in compounding the present compositions may be any suitable polymer which is hydrophilic and water-dispersible, has free carboxylic groups and relatively high base binding capacity, and forms a gel of substantially uniform consistency when neutralized with a base. Preferred polymers for use in the compositions of the invention are water-dispersible polycarboxylated vinyl polymers. Polyacrylic acid polymers are particularly preferred for the present purposes. The molecular weight of the polymer is desirably in the range of about 1,250,000 and about 4,000,000. Suitable polyacrylic acid polymers include, but are not limited to,

polyacrylic acid polymers lightly crosslinked with a polyalkenyl polyether such as those commercially available from B.F. Goodrich, Cincinatti, Ohio, under the trademarks Carbopol 934, 940, and 941. Carbopol 940™ is a particularly preferred polymer for use in practicing this invention.

The polymer is present in an amount sufficient to cause gelling of the composition and impart the desired viscous consistency to the topical formulation. The metronidazole compositions advantageously comprise about 0.2% to about 7.0% by weight of the polymer, preferably about 0.5% to about 1.5%, and most preferably about 0.6% by weight of the polymer based on the total weight of the composition.

Aqueous solutions of these polymers form gels when neutralized with a base. Water-soluble bases which have been used to promote gelling of polymers such as Carbopols™ include inorganic bases such as an aqueous solution of ammonia, NaOH, and organic amines, e.g., alkylamines such as methylamine and ethylamine, dialkylamines, trialkylamines, alkanolamines, dialkanolamines, and the like. The effective component of the compositions of the present invention, metronidazole, is sufficiently basic to partially neutralize the acidic polymer in aqueous solution to the desired degree and to promote gelling.

Optionally, the composition may further include a "penetration enhancer", i.e., an agent that promotes penetration of the active drug into the patient's skin or tissues. Such penetration enhancers include but are not limited to, dimethyl sulfoxide (DMSO) and propylene glycol, with the latter being preferred. The composition advantageously includes about 1.0% to about 50%,

preferably about 2% to about 5%, and more preferably about 3% by weight of said penetration enhancer, based on the total weight of the composition.

Preservatives optionally may be incorporated into the compositions in an amount effective for inhibiting growth of microbes such as yeast and molds in the composition during storage. Any conventional preservatives may be used, with parabens being preferred. A mixture of methyl paraben and propyl paraben has been found particularly effective as a preservative. Most preferably, the composition comprises about 0.08% by weight of methyl paraben and about 0.02% by weight of propyl paraben based on the total weight of the composition.

Ethylenediaminetetraacetic acid (EDTA) or one of its salts is commonly added to dermatological preparations, and may optionally be incorporated into the compositions of the present invention. EDTA chelates certain metals that may be present in the formulation, which is useful because some patients have adverse reactions to preparations containing metal impurities. The EDTA will also inhibit undesirable "browning" of the composition which may occur over time in compositions having a low pH value, e.g., a pH value of about 3.5 to about 5.4. Advantageously, the formulation of the invention optionally further includes from about 0.01% to about 0.1%, preferably about 0.05% by weight of EDTA based on the total weight of the composition.

The final pH value of the formulations of the invention may vary within a physiologically compatible range. Advantageously, the final pH value is a physiologically compatible, i.e., not harmful to biological tissue, acidic pH value. The pH value is preferably between about 3 and about 6.9, and most

preferably between about 4 and 5. Any suitable method of adjusting the pH value of aqueous solutions may be used. Advantageously, sodium hydroxide (NaOH) is added to the composition to bring the final pH value to the desired level. Gel compositions of the invention are more viscous at pH values that approach neutrality than at the more acidic pH values within the preferred range, i.e., viscosity increases as the polymer in the gel is neutralized to a greater degree, e.g., with NaOH.

The ingredients listed above may be combined in any order and manner that produces a composition comprising metronidazole dissolved in, and evenly dispersed throughout, a one-phase aqueous gel of the desired consistency and pH value. One suitable method of preparing compositions of the invention involves preparation of an aqueous solution of the polymer, which will be called "Part A". Advantageously, this solution comprises the polymer in distilled water. A "Part B" is prepared comprising metronidazole. Mixing of Parts A and B results in gelling of the composition. The optional penetration enhancer and preservative(s) are preferably included in Part B. If EDTA is to be added to the formulation, it is preferably included in Part A. The pH value may then be adjusted to the desired level, e.g., by addition of NaOH.

The resulting homogeneous gels possess the advantageous properties described above, including utilizing non-comedogenic, non-acneogenic, and non-irritating ingredients; higher specific activity of metronidazole due to increased diffusion across membranes and release from the vehicle which results in greater therapeutic effectiveness using smaller amounts of metronidazole; and a desirable consistency

that prevents undesired pooling and spreading of metronidazole. High concentrations of skin-drying ingredients (e.g. alcohols and acetone), which are found in some dermatological preparations to promote drug solubility, are also avoided. Such ingredients at high concentration may excessively dry the patient's skin, causing undesirable flaking and discomfort.

The therapeutic effectiveness of the metronidazole compositions of the present invention is demonstrated in the following examples. These examples are meant to illustrate the invention rather than to limit its scope. Variations in the compositions which do not adversely affect the effectiveness of metronidazole will be evident to one skilled in the art, and are within the scope of this invention. For example, additional ingredients such as coloring agents, sunscreens, and the like may be included in the compositions as long as the resulting composition retains the desirable properties, e.g., non-comedogenicity, high specific activity, and the like, described above.

EXAMPLE I

A 30 kilogram batch of a composition of the present invention was prepared as follows. 180 Grams of Carbopol 940™ (0.6% by weight of the final weight of the composition) was dissolved in 16.5 liters of distilled water containing 15 grams of ethylenediaminetetraacetic acid (EDTA) disodium dihydrate. Sufficient amount of 10 wt-% sodium hydroxide (NaOH) solution was added to bring the pH value to about 5. This aqueous polymer solution was called "Part A". "Part B" was prepared by mixing 900 grams of propylene glycol (3% by weight of the final weight of the composition), 24 grams of methyl

paraben (0.08% by weight of the final weight of the composition) and 6.0 grams of propyl paraben (0.02% by weight of the final weight of the composition). The mixture was added to 225 grams of metronidazole dispersed in 11.4 liters of distilled water maintained at 50°C. Parts A and B were then mixed thoroughly and gelling of the composition resulted. A cold aqueous solution of NaOH was then used to adjust the final pH value to 5.25. Distilled water was then added to give the desired 30 kilogram final weight. The NaOH and water were thoroughly mixed into the viscous gel.

A random, double blind, placebo controlled clinical trial was conducted to demonstrate the positive clinical efficacy of the aqueous metronidazole-containing gel composition prepared in Example I in treating rosacea. The study included patients who had received no prior treatment for rosacea, as well as patients who had been treated by conventional methods. Patients discontinued treatment, if any, at least 21 days prior to the start of this study. Each patient received metronidazole in the gel composition on one side of the face and the gel composition (placebo control) without metronidazole on the other side of the face. Therefore, in this study, each patient served as their own control.

The effectiveness of the treatment was rated, at the time points indicated in the TABLES below, in six different categories, namely, reduction in inflammatory lesions (papules and pustules), erythema, stinging, burning, itching, and dryness. The data are shown in the TABLES below.

TABLE I-A shows the percent reduction in inflammatory lesions (papules and pustules) from baseline values for active (i.e., metronidazole-treated) and placebo-treated sides. Inflammatory lesions were progressively reduced from 46.7% to 59.9% for active-treated sides while placebo-treated sides reflected an exacerbation. There was an 82.6% difference in inflammatory lesions at the end of drug treatment on the metronidazole versus placebo-treated sides.

TABLE I-B shows mean erythema values for active and placebo-treated sides. Statistically significant differences were found at visits 2, 3, 4 and 5 for the active sides and at visits 3 and 4 for the placebo sides, when compared to baseline values. Active and placebo-side values were significantly different from each other at visits 3, 4 and 5. A concommitant improvement in reduction of erythema was seen at the same time point on the treated side and on the placebo side.

Tables II-A, II-B, II-C, and II-D show an unexpected but dramatic improvement in local tolerance data. This data represents the patients' subjective assessments of stinging, burning, itching and dryness on each side of their faces before and during drug or placebo treatment. The data shows that there was a dramatic (highly statistically significant) improvement in the patients' perceptions of these attendant complications of the disease. Since both sides improved to the same degree, i.e., no statistically significant difference can be found, the improvement apparently comes from the gel composition per se.

TABLE II-A shows mean stinging scores for active and placebo-treated sides. Statistically

significant differences were found at visits 3, 4 and 5 for both the active and placebo sides, when compared to baseline values. Active and placebo-side values were not significantly different from one another.

TABLE II-B shows mean burning scores for active and placebo-treated sides. Statistically significant differences were found at all visits (2, 3, 4, 5) for both the active and placebo sides, when compared to baseline values. Active and placebo-side values were not significantly different from one another.

TABLE II-C shows mean itching scores for active and placebo-treated sides. Statistically significant differences were found at all visits (2, 3, 4, 5) for both the active and placebo sides, when compared to baseline values. Active and placebo-side values were not significantly different from one another.

TABLE II-D shows mean dryness scores for active and placebo-treated sides. Statistically significant differences were found at visits 3, 4 and 5 for active sides and at visits 4 and 5 for placebo sides, when compared to baseline values. Active and placebo-side values were not significantly different from one another.

This data confirms the effectiveness of metronidazole in the gel composition for treatment of rosacea and also demonstrates the unique therapeutic effects of the gel composition.

TABLE I-A

Inflammatory Lesions

(Efficacy Data From 20 Subjects)

| | On Drug | | | Off Drug |
|---|---|---|---|---|
| | Visit 2 Weeks 3-5 | Visit 3 Weeks 6-8 | Visit 4 Weeks 9-11 | Visit 5 Weeks 12-17 |
| Active (Percent Reduction from Baseline) | 46.7 | 55.1 | 59.9 | 41.6 |
| Placebo (Percent Reduction from Baseline) | -22.5 | -4.2 | -22.7 | -46.8 |
| Difference (Active-Placebo Percent Difference) | 69.2 | 59.3 | 82.6 | 88.4 |

TABLE I-B

Erythema

(Efficacy Data From 20 Subjects)

| | | On Drug | | | | Off Drug |
|---|---|---|---|---|---|---|
| | Visit 1 Baseline | Visit 2 Weeks 3-5 | Visit 3 Weeks 6-8 | Visit 4 Weeks 9-11 | Visit 5 Weeks 12-17 |
| Active (Mean Values | 2.10 | 1.55**** | 1.05*** | 1.05*** | 1.15*** |
| Placebo (Mean Values | 2.10 | 1.90 | 1.55*** | 1.55*** | 1.70 |

3=Severe
2=Moderate
1=Mild
0=Absent

*** p<0.01 compared to baseline values.

| | | | | | |
|---|---|---|---|---|---|
| Active Versus Placebo Significant Differences (p values) | None | None | p<0.02 | p<0.02 | p<0.02 |

TABLE II-A

Stinging

(Local Tolerance Data from 20 Subjects)

| | On Drug | | | | Off Drug |
|---|---|---|---|---|---|
| | Visit 1 Baseline | Visit 2 Weeks 3-5 | Visit 3 Weeks 6-8 | Visit 4 Weeks 9-11 | Visit 5 Weeks 12-17 |
| Active (Mean Values | 0.70 | 0.25 | 0.15** | 0.00*** | 0.00*** |
| Placebo (Mean Values | 0.65 | 0.30 | 0.15* | 0.20* | 0.05*** |
| 3=Severe 2=Moderate 1=Mild 0=Absent | | | | | |
| * $p<0.05$ compared to baseline values. | | | | | |
| ** $p<0.02$ compared to baseline values | | | | | |
| *** $p<0.01$ compared to baseline values | | | | | |
| Active Versus Placebo Significant Differences (p values) | None | None | None | None | None |

TABLE II-B

Burning

(Local Tolerance Data from 20 Subjects)

| | On Drug | | | | Off Drug |
|---|---|---|---|---|---|
| | Visit 1 Baseline | Visit 2 Weeks 3-5 | Visit 3 Weeks 6-8 | Visit 4 Weeks 9-11 | Visit 5 Weeks 12-17 |
| Active (Mean Values | 1.25 | 0.30** | 0.10*** | 0.05*** | 0.05*** |
| Placebo (Mean Values | 1.05 | 0.30*** | 0.05*** | 0.10*** | 0.05*** |

3=Severe
2=Moderate
1=Mild
0=Absent

** $p < 0.02$ compared to baseline values.

*** $p < 0.01$ compared to baseline values

| | | | | | |
|---|---|---|---|---|---|
| Active Versus Placebo Significant Differences (p values) | None | None | None | None | None |

TABLE II-C

Itching

(Local Tolerance Data from 20 Subjects)

| | | On Drug | | | Off Drug |
|---|---|---|---|---|---|
| | Visit 1 | Visit 2 | Visit 3 | Visit 4 | Visit 5 |
| | | Weeks | Weeks | Weeks | Weeks |
| | Baseline | 3-5 | 6-8 | 9-11 | 12-17 |
| Active (Mean Values | 1.45 | 0.55*** | 0.15*** | 0.20*** | 0.10*** |
| Placebo (Mean Values | 1.40 | 0.70*** | 0.25*** | 0.20*** | 0.15*** |

3=Severe
2=Moderate
1=Mild
0=Absent

*** p<0.01 compared to baseline values

Active Versus Placebo Significant Differences (p values) None None None None None

TABLE II-D

Dryness

(Local Tolerance Data from 20 Subjects)

| | On Drug | | | | Off Drug |
|---|---|---|---|---|---|
| | Visit 1 Baseline | Visit 2 Weeks 3-5 | Visit 3 Weeks 6-8 | Visit 4 Weeks 9-11 | Visit 5 Weeks 12-17 |
| Active (Mean Values | 1.45 | 0.85 | 0.50*** | 0.25*** | 0.25*** |
| Placebo (Mean Values | 1.40 | 0.85 | 0.75 | 0.20*** | 0.45*** |
| 3=Severe 2=Moderate 1=Mild 0=Absent | | | | | |
| *** $p<0.01$ compared to baseline values | | | | | |
| Active Versus Placebo Significant Differences (p values) | None | None | None | None | None |

A study was conducted to determine differences in the in-vitro release characteristics of metronidazole from various topical compositions using the following experimental procedure.

The metronidazole gel or cream was placed into a shallow well about 1 millimeter deep created

by a Plexiglass™ template placed on a round 5.2 centimeter Plexiglass™ base. The diameter of the template into which the composition was placed was 3.0 centimeters. The composition was covered by a piece of Spectrapor™ membrane (available from Spectrum Medical Industries, Inc., Los Angeles, CA 90054) having a molecular weight cutoff of between 12,000 and 14,000. The membrane had been soaked in a buffer having a pH value of 5.5 for 24 hours. A second template identical in size to the template forming the well was utilized to hold the membrane in place. The templates were secured by four nylon screws thereby creating a holder. 400 Cubic centimeters of an acetate buffer solution having a pH value of 5.5 was placed in a round bottom dissolution flask (available from Hanson Research Corporation, Northridge, CA 91324) and the temperature of the solution was equilibrated to 32°C. A solid halogenated hydrocarbon polymer-coated stirrer was lowered into a position 2.54 centimeters above the membrane surface. The solution was stirred at 50 RPM. Five cubic centimeter samples were removed at 5, 10, 15, 20, 30, 40, and 60 minutes. The volume of the sample was replaced each time with fresh solution. The samples were analyzed at 319 nanometers on a spectrophotometer (Model 8450A, Hewlett-Packard, Palo Alto, CA 94303).

After absorbance was converted to concentration using a Beer's Law plot, the total milligrams of metronidazole released at each time point was calculated from the following equation:

$$\text{Metronidazole released (mg)} = \frac{[\text{Concentration } (\mu\text{mg/cc})] \times [400]}{[1000 \text{ micrograms/milligrams}]}$$

Additional compositions that have been studied are shown in TABLE III, below. These compositions were prepared in substantially the same manner as described in Example I, above.

TABLE III
Compositions, in wt. %

| Components | C1 | C2 | C3 |
|---|---|---|---|
| Metronidazole | 0.75 | 0.75 | 1.00 |
| Propylene Glycol | 3.00 | - | - |
| Polyacrylic Acid Polymer [1] | 0.60 | 0.60 | - |
| Methyl Paraben | 0.08 | 0.08 | - |
| Propyl Paraben | 0.02 | 0.02 | - |
| Disodium EDTA | 0.05 | 0.05 | - |
| Cetylane | - | - | 5.00 |
| Cetyl Alcohol | - | - | 15.00 |
| Sodium Lauryl Sulfate | - | - | 1.50 |
| Lactic Acid | - | - | 1.50 |
| Water, q.s. ad | 100.00 | 100.00 | 100.00 |

[1] Carbopol 940 from B.F. Goodrich Company, a commercially available polyacrylic acid polymer.

Data from three trials for the release of metronidazole from C1, a gel composition, (0.75 wt-% metronidazole; pH value about 5.8) are presented in TABLE IV and are plotted in FIGURE 1. In FIGURE 1, Trial One is denoted by (o), Trial Two by (•) and Trial Three by (x). The average data for the three trials is presented in TABLE VII and is plotted in FIGURE 2. Traditional linear plots for release of

drugs from ointment bases are obtained by plotting amount released vs. the square root of time.

TABLE IV

Release of Metronidazole from C1 (mg)

| Time (Min) | Trial One | Trial Two | Trial Three |
|---|---|---|---|
| 0 | 0 | 0 | 0 |
| 5 | 1.37 | 1.26 | 1.33 |
| 10 | 2.09 | 2.14 | 2.14 |
| 15 | 2.96 | 2.86 | 2.86 |
| 20 | 3.54 | 3.47 | 3.44 |
| 30 | 4.50 | 4.54 | 4.38 |
| 40 | 5.19 | 5.34 | 5.10 |
| 60 | 6.16 | 6.53 | 6.09 |

Data from three trials for the release of metronidazole from C2, another gel composition, (0.75 wt-% metronidazole, without propylene glycol; pH value about 5.8) are presented in TABLE V and are plotted in FIGURE 3. In FIGURE 3, Trial One is denoted by (o), Trial Two by (●) and Trial Three by (x). The average data for the three trials is presented in TABLE VII and are plotted in FIGURE 4. Again, traditional linear plots for release of drugs from ointment bases are obtained by plotting amount released vs. the square root of time.

TABLE V

Release of Metronidazole from C2 (mg)

| Time (Min) | Trial One | Trial Two | Trial Three |
|---|---|---|---|
| 0 | 0 | 0 | 0 |
| 5 | 1.21 | 1.27 | 1.39 |
| 10 | 2.02 | 2.18 | 2.29 |
| 15 | 2.70 | 2.95 | 3.04 |
| 20 | 3.29 | 3.89 | 3.67 |
| 30 | 4.30 | 4.62 | 4.75 |
| 40 | 5.02 | 5.32 | 5.57 |
| 60 | 6.15 | 6.41 | 6.69 |

Data from three trials for the release of the metronidazole from C3, a cream composition, (1.0 wt-% metronidazole; pH value about 3.2) are presented in TABLE VI and are plotted in FIGURE 5. In FIGURE 5, Trial One is denoted by (o), Trial Two by (•) and Trial Three by (x). The average data for the three trials are presented in TABLE VII and are plotted in FIGURE 6. Again, traditional linear plots for release of drugs from ointment bases are obtained by plotting amount released vs. the square root of time.

TABLE VI

Release of Metronidazole from C3 (mg)

| Time (Min) | Trial One | Trial Two | Trial Three |
|---|---|---|---|
| 0 | 0 | 0 | 0 |
| 5 | 0.56 | 0.42 | 0.46 |
| 10 | 0.78 | 0.67 | 0.66 |
| 15 | 0.94 | 0.85 | 0.82 |
| 20 | 1.09 | 0.98 | - |
| 30 | 1.32 | 1.25 | 1.29 |
| 40 | 1.53 | 1.54 | 1.63 |
| 60 | 1.94 | 1.82 | 1.69 |

TABLE VII

Average Release of Metronidazole (mg)

| Time (Min) | C1 | C2 | C3 |
|---|---|---|---|
| 0 | 0 | 0 | 0 |
| 5 | 1.32 ± 0.06 | 1.29 ± 0.09 | 0.48 ± 0.07 |
| 10 | 2.12 ± 0.03 | 2.16 ± 0.14 | 0.70 ± 0.07 |
| 15 | 2.89 ± 0.06 | 2.90 ± 0.18 | 0.87 ± 0.06 |
| 20 | 3.48 ± 0.05 | 3.62 ± 0.30 | 1.04 ± 0.08 |
| 30 | 4.47 ± 0.08 | 4.56 ± 0.23 | 1.29 ± 0.04 |
| 40 | 5.21 ± 0.12 | 5.30 ± 0.28 | 1.57 ± 0.06 |
| 60 | 6.26 ± 0.24 | 6.42 ± 0.27 | 1.82 ± 0.13 |

TABLE VIII and FIGURE 7 show, for comparison purposes, the average metronidazole released from C1 (o), C2 (x) and C3 (•). The large difference in the slopes of the plots indicate that the release rate of the gel compositions, i.e., C1 and C2, is about 3.7 times greater than that from the cream, i.e., C3.

TABLE VIII

Comparison of the Release Rates (Slopes) of the Three Compositions

| Composition | Release Rates ($mg/min^{(1/2)}$) |
|---|---|
| C1 | 0.9166 ± 0.0492 |
| C2 | 0.9465 ± 0.0349 |
| C3 | 0.2505 ± 0.0071 |

The in-vitro release of metronidazole from the gel formulations with or without propylene glycol is either 3.66 or 3.78 times faster, respectively, than that of the metronidazole from the cream formulation C3.

The foregoing specification is intended as illustrative and is not to be taken as limiting. Still other variations within the spirit and the scope of the invention are possible and will readily present themselves to those skilled in the art.

I CLAIM:

1. A dermatological preparation for topical application in the form of an aqueous gel composition comprising:

a therapeutically effective amount of metronidazole;

a gelled, hydrophilic and water-dispersible polymer having free carboxylic groups; and

an aqueous solvent for said metronidazole.

2. The preparation in accordance with claim 1 wherein the concentration of said metronidazole is at least about 0.1 percent by weight based on the total weight of said composition.

3. The preparation in accordance with claim 2 wherein the concentration of said metronidazole present is in the range of about 0.25 percent to about 1.0 percent by weight based on the total weight of said composition.

4. The preparation in accordance with claim 3 wherein the concentration of said metronidazole present is about 0.75 percent by weight based on the total weight of said composition.

5. The preparation in accordance with claim 1 wherein said polymer is a hydrophilic, water-dispersible polycarboxylated vinyl polymer.

6. The preparation in accordance with claim 5 wherein said vinyl polymer is a polyacrylic acid polymer having a molecular weight in the range of about 1,250,000 to about 4,000,000 daltons.

7. The preparation in accordance with claim 1 wherein said polymer is present in a range of about 0.2 percent to about 7.0 percent by weight based on the total weight of said composition.

8. The preparation in accordance with claim 7 wherein said polymer is present in a range of

about 0.5 percent to about 1.5 percent by weight based on the total weight of said composition.

9. The preparation in accordance with claim 8 wherein said polymer is present in an amount of about 0.6 percent by weight based on the total weight of said composition.

10. The preparation in accordance with claim 1 further including a penetration enhancer.

11. The preparation in accordance with claim 10 wherein said penetration enhancer is propylene glycol present in a range of about 2 percent to about 5 percent by weight based on the total weight of said composition.

12. The preparation in accordance with claim 11 wherein said penetration enhancer is present in an amount of about 3 percent by weight based on the total weight of the composition.

13. The preparation in accordance with claim 1 further including a preservative.

14. The preparation in accordance with claim 13 wherein said preservative comprises at least one paraben.

15. The preparation in accordance with claim 14 wherein said preservative is methyl paraben present in an amount about 0.08 weight percent and propyl paraben present in an amount of about 0.02 weight percent, based on the total weight of said composition.

16. The preparation in accordance with claim 1 further including ethylenediaminetetraacetic acid in a range of about 0.01 percent to about 0.1 percent by weight based on the total weight of said compositon.

17. A method for treatment of a human afflicted with a skin disorder, said method

comprising topically applying to the afflicted skin a therapeutically effective amount of a dermatological preparation in the form of an aqueous gel composition comprising:

a therapeutically effective amount of metronidazole;

a gelled, hydrophilic and water-dispersible polymer having free carboxylic groups; and

an aqueous solvent of said metronidazole.

18. The method of claim 17 wherein said skin disorder is rosacea.

19. The method 17 wherein said skin disorder is acne vulgaris.

20. The method of claim 17 wherein skin disorder is one from the group comprising steroid acne, acne conglobata, nodulocystic acne, perioral dermatitis, and seborrheic detmatitis.

FIG. 1

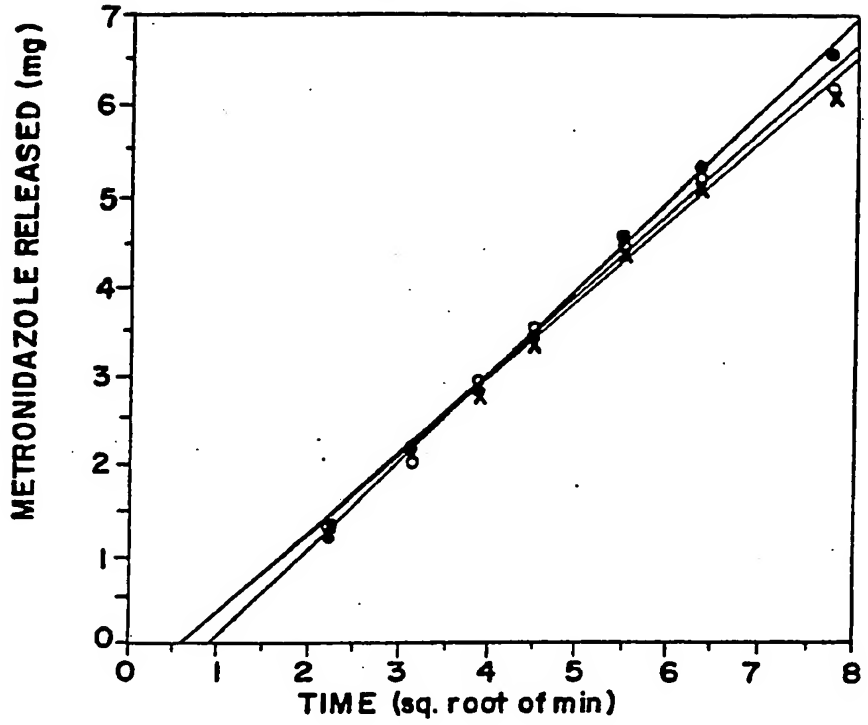

METRONIDAZOLE RELEASED (mg)
TIME (sq. root of min)
0
1
2
3
4
5
6
7
8

FIG. 2

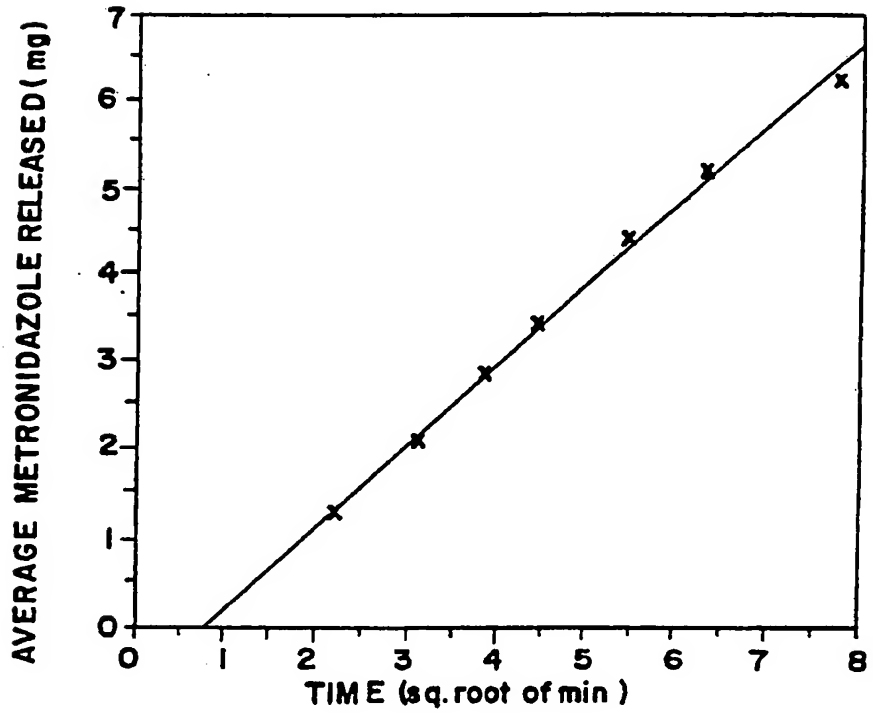

AVERAGE METRONIDAZOLE RELEASED (mg)
TIME (sq. root of min)
0
1
2
3
4
5
6
7
8

FIG. 3.

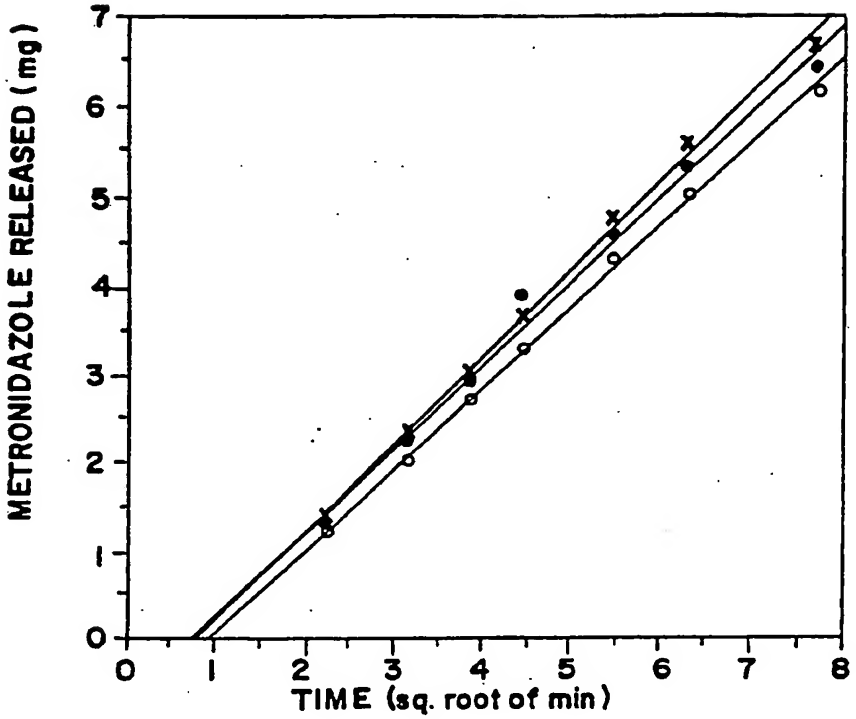
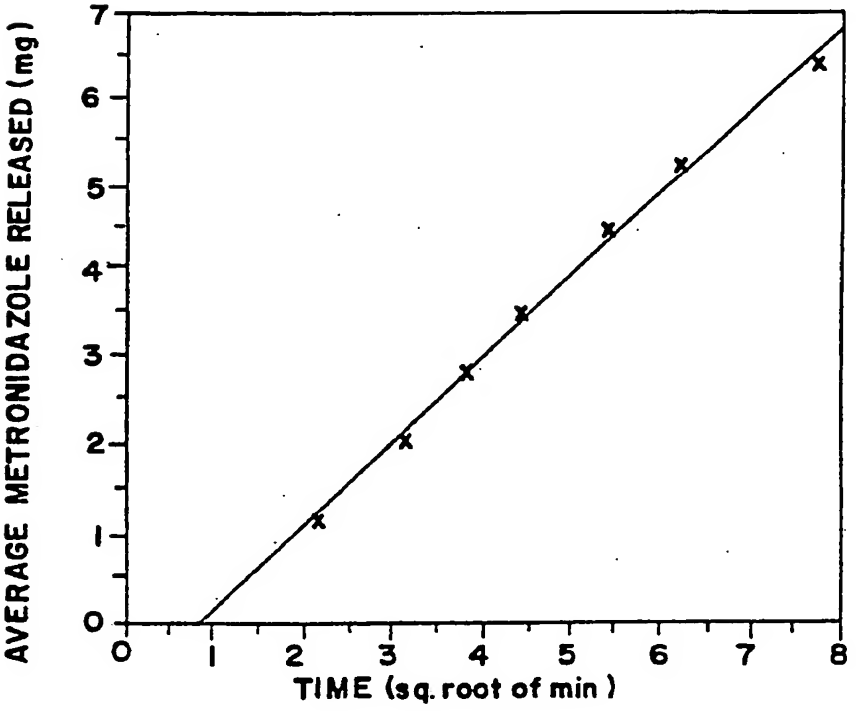

METRONIDAZOLE RELEASED (mg)
TIME (sq. root of min)
0
1
2
3
4
5
6
7
8

FIG. 4.


AVERAGE METRONIDAZOLE RELEASED (mg)
TIME (sq. root of min)
0
1
2
3
4
5
6
7
8

3/4

FIG_5_

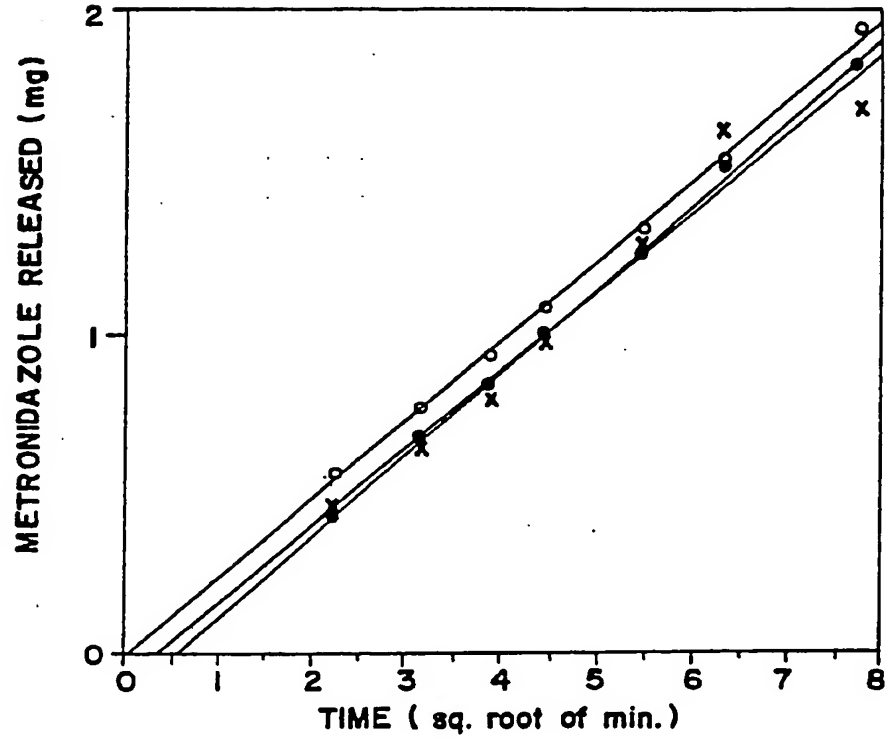

METRONIDAZOLE RELEASED (mg)
TIME ( sq. root of min.)
0
1
2
0
1
2
3
4
5
6
7
8

FIG_6_

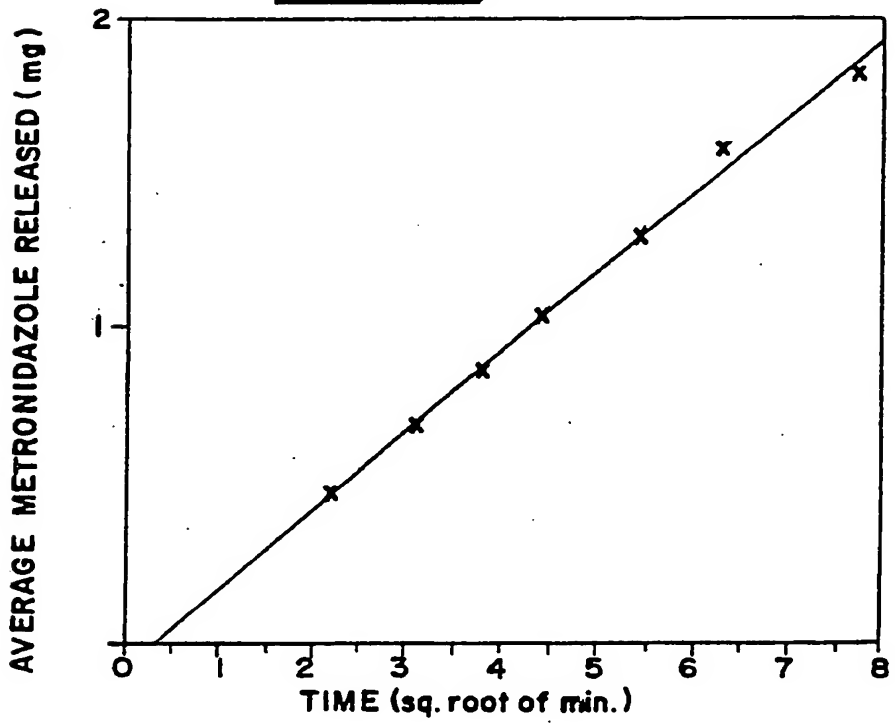
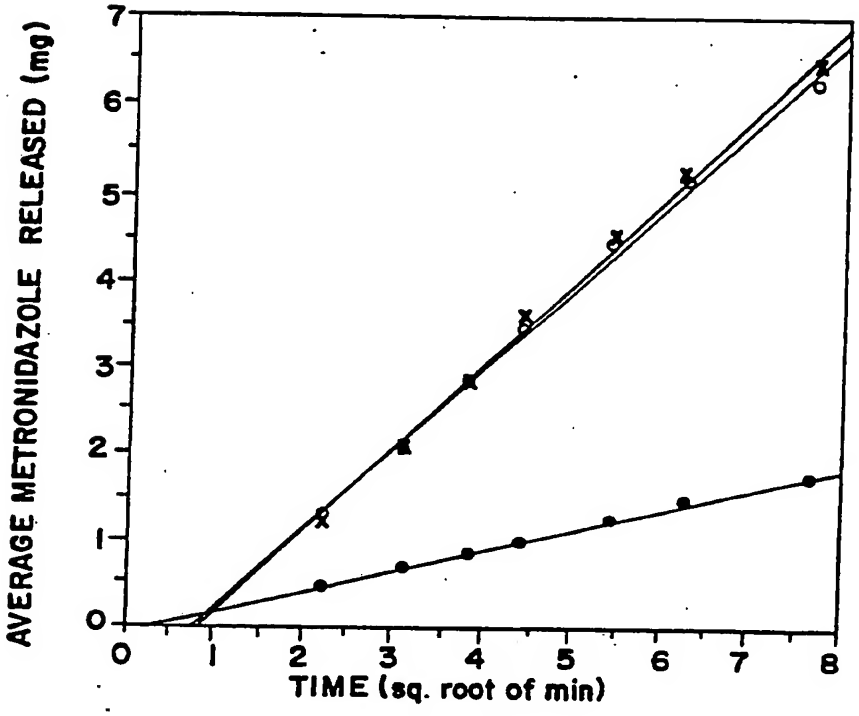

AVERAGE METRONIDAZOLE RELEASED (mg)
TIME (sq. root of min.)
0
1
2
0
1
2
3
4
5
6
7
8

Fig-7-


AVERAGE METRONIDAZOLE RELEASED (mg)
0
1
2
3
4
5
6
7
TIME (sq. root of min)
0
1
2
3
4
5
6
7
8

# INTERNATIONAL SEARCH REPORT

International Application No. PCT/US89/00116

## I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC(4): A61K 31/78 A 61K 31/415

U.S. CL. 424/81, 514/398, 514/859, 514/944

## II. FIELDS SEARCHED

Minimum Documentation Searched [7]

| Classification System | Classification Symbols |
|---|---|
| U.S. | 424/81, 514/398, 514/398, 514/859, 514/944 |

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched [8]

Chemical Abstracts (U.S.A.) 1967-1988 under Heading:
IH Imidazole-1-ethanol, 2-methyl, 5-Nitro

## III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

| Category * | Citation of Document, [11] with indication, where appropriate, of the relevant passages [12] | Relevant to Claim No. [13] |
|---|---|---|
| Y | Physicians Desk Reference, 38 ed., 1984, Pub. Medical Economics Co., Inc., USA, Page 1637 See product "PERSA-GEL" | 1-20 |
| Y | Nielsen, British Journal of Dermatology, vol. 109 1983, pages 63 to 65, see entire document | 1-20 |
| Y | Jillison, Cutis, USA, vol. 34, November 1984, pages 457 and 458. See entire document. | 1-20 |

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

## IV. CERTIFICATION

| Date of the Actual Completion of the International Search | Date of Mailing of this International Search Report |
|---|---|
| 5 April 1989 | 11 MAY 1989 |
| **International Searching Authority** | **Signature of Authorized Officer** |
| ISA/US | LEONARD SCHENKMAN |

Form PCT/ISA/210 (second sheet) (Rev.11-87)